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CONTENTS OF VOLUME XVIII

No. 1. *MARCH, 1959*

	PAGE
Role of Hypersensitivity in the Pathogenesis of Rheumatoid Arthritis. Heberden Oration, 1958. CHARLES RAGAN	1
Resorption of Intracutaneously Injected Congo Red. R. A. PARKINS and E. G. L. BYWATERS	8
Ankylosing Spondylitis in Women. F. DUDLEY HART and K. C. ROBINSON	15
Significance of the Waaler-Rose Test, Streptococcal Agglutination, and Antistreptolysin Titre in the Prognosis of Rheumatoid Arthritis. H. A. OTTEN and F. WESTENDORP BOERMA	24
Indications for Surgical Intervention in Rheumatoid Arthritis of the Wrist and Hand. J. C. F. CREGAN	29
Effect of Intramuscular Injection of Pituitary Tissue in Rheumatoid Arthritis. P. FORGÁCS, L. BAKOS, G. CSASZAR, and E. RIESZ	34
Reiter's Disease in the Female. J. K. OATES and GEORGE W. CSONKA	37
"Rheumatic" Iritis and Iridocyclitis. F. LENOCH, V. KRÁLÍK, and J. BARTOŠ	45
Diagnostic Criteria for Rheumatoid Arthritis. 1958 Revision	49
Heberden Society	54
Book Review	68
Ligue Européenne contre le Rhumatisme	68
Società Italiana di Reumatologia	68
New Zealand Rheumatism Association	69
Abstracts	71

No. 2. *JUNE, 1959*

Treatment of Rheumatoid Arthritis by a Sanatorium Regime. R. M. MASON and W. G. WENLEY	91
Corticotrophin (ACTH) in Rheumatoid Arthritis. O. SAVAGE, P. S. DAVIS, L. CHAPMAN, J. WICKINGS, J. D. ROBERTSON, and W. S. C. COPEMAN	100
Lesions of Joints and Tendon Sheaths in Systemic Lupus Erythematosus. BRUCE CRUICKSHANK	111
Trials of Cortisone Analogues in the Treatment of Rheumatoid Arthritis. H. W. FLADEE, G. R. NEWNS, W. D. SMITH, and H. F. WEST	120
Metabolism of Connective Tissue in Limb Atrophy in the Rabbit. JAMES W. BROOKE and H. G. BEWICK SLACK	129
Effect of Aspirin on Cutaneous Response to the Local Application of an Ester of Nicotinic Acid. LESLIE H. TRUELOVE and J. J. R. DUTHIE	137
Empire Rheumatism Council. Twenty-Second Annual Report	142
Heberden Society	145
B.M.A. Joint Annual Meeting with C.M.A.	148
Canadian Rheumatism Association	148
Argentine League against Rheumatism	148
European League against Rheumatism	149
Turkish Association for Rheumatism Research and Treatment	149
British Rheumatic Association	149
New York Rheumatism Association	149
Abstracts	150

No. 3. *SEPTEMBER, 1959*

PAGE

A Comparison of Prednisolone with Aspirin or other Analgesics in the Treatment of Rheumatoid Arthritis. M. R. C. Report 173

A Method for Testing Analgesics in Rheumatoid Arthritis using a Sequential Procedure. J. HAJNAL, J. SHARP, and A. J. POPERT 189

An Immuno-Histological Study of Connective Tissue. D. G. SCOTT 207

Serum Complement, Rheumatoid Factor, and Other Serum Proteins in Rheumatoid Disease and Systemic Lupus Erythematosus. H. A. ELLIS and D. FELIX-DAVIES 215

Differential Agglutination Titre (D.A.T.) in Juvenile Rheumatoid Arthritis. E. G. L. BYWATERS, MARY E. CARTER, and F. E. T. SCOTT 225

Comparison of Differential Agglutination Titre (D.A.T.) in Juvenile and Adult Rheumatoid Arthritis. E. G. L. BYWATERS, MARY E. CARTER, and F. E. T. SCOTT 233

Urinary Excretion of Acid Polysaccharide in Rheumatoid Arthritis and Other Diseases. G. LOEWI 239

Controlled Trial of G27 202 (*p*-Hydroxyphenylbutazone) in Rheumatoid Arthritis. NEIL CARDOE 244

Tietze's Syndrome. J. LANDON and J. S. MALPAS 249

Nucleoprotein-Latex Agglutination Test in Connective Tissue Diseases. W. J. FESSEL 255

Heberden Society 259

Book Review 264

Società Italiana di Reumatologia. Acqui Prizes, 1959 264

Abstracts 265

No. 4. *DECEMBER, 1959*

Familial Incidence of Rheumatoid Arthritis. JOAN M. BREMNER, W. R. M. ALEXANDER, and J. J. R. DUTHIE 279

Acute Rheumatic Fever in Young Men. J. D. H. SLATER and S. ROSENBAUM 285

Differences between the Fever of Still's Disease and that of Rheumatic Fever. F. J. MCMINN and E. G. L. BYWATERS 293

Salicylates and the Adrenal Cortex. M. J. H. SMITH 298

Experience with British Latex Suspension for Agglutination Tests in Rheumatoid Arthritis. HARRY COKE 301

Evaluation of an Epidemiological Method. STEPHEN E. MALAWISTA, LAWRENCE R. BOIES, and S. WARREN SEIDES 305

Anti-Inflammatory Effect of Obstructive Jaundice in Rats. RONALD L. ENGERMAN and ROLAND K. MEYER 309

Urinary Indoles and other "Ehrlich's Reagent Reactors" in Rheumatoid Arthritis. MARTTI OKA and V. V. E. LEPPÄNEN 313

Importance of an Increased Gamma Globulin Level in the Determination of Gm Groups in Collagen Diseases. H. JULKUNEN and ANJA TIILIKAINEN 318

Comparative Study of the Haemagglutination Test and a Simple Latex-Fixation Test for the Detection of the Rheumatoid Factor. G. MORGAN 322

Comparison of Intra-Articular Cortisone Analogues in Osteo-Arthritis of the Knee. M. J. KEHR .. 325

Book Review 329

Canadian Rheumatism Association 329

Heberden Society 330

Ligue Européenne contre le Rhumatisme 332

Abstracts 333

Index 355

Ann. rheum. Dis. (1959), **18**, 1.

PAGE
173
189
207
215
225
233
239
244
249
255
259
264
264
265
279
285
293
298
301
305
309
313
318
322
325
329
329
330
332
333
355

HEBERDEN ORATION, 1958

ROLE OF HYPERSENSITIVITY IN THE PATHOGENESIS OF RHEUMATOID ARTHRITIS*

BY

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William Heberden published his description of angina pectoris 192 years ago (Major, 1932). There are certain similarities between his thinking on this subject and our present approach to rheumatoid arthritis. Both are descriptive with glimmerings of possible pathogenic mechanisms. To-day, I propose to consider one such mechanism and I hope that my humility will be as obvious as was Heberden's.

This discussion will pose a question, present the available evidence, and offer a tentative conclusion. It will be obvious that further data must be obtained before a final satisfactory conclusion can be reached.

The question to be raised is "What is the pathogenesis of peripheral joint rheumatoid arthritis?" We shall, of course, be limited to pathogenic mechanisms that might explain a self-perpetuating disease characterized by inflammation associated with the formation of granulomata. Hill (1958), in discussing the aetiology of this disease, has pointed out that no hypothesis rests on more than a few loosely connected pieces of evidence. He has summarized in excellent fashion the four chief theories. These are infection and focal sepsis, metabolic abnormality, endocrine abnormality, and hypersensitivity. The last is currently the most attractive hypothesis and will be the subject of this discussion.

We are concerned solely with peripheral joint rheumatoid arthritis, excluding all variants such as spondylitis, the arthritis associated with psoriasis, ulcerative colitis, and Reiter's syndrome. Clinically, the disease covers a wide spectrum of severity and variability. It is a disease which, as far as we know, appears only in human beings. Although a female preponderance has been noted in most hospital studies (Ragan, 1949; Short, Bauer, and Reynolds, 1957), recent epidemiological work (Kellgren and Lawrence, 1956) involving whole populations has shown that the sex incidence of sero-positive and *x*-ray proven rheumatoid arthritis approaches a 1 : 1 ratio. Patients with clinical manifestations alone, however, show the same female preponderance. Age distribution is wide, with peaks in females appearing around the menopause in some series (Short and others, 1957) and at the ages of 35 and 45 in others (Clemmensen and Arnsø, 1952). Isolated instances have been described with onset at the age of 80 and, at the other extreme, in the first year of life. This is in contrast to rheumatic fever where the onset before the age of 3 or 4 years is extremely rare. No adequate data are available concerning geographic distribution. However, it may be noted that a group of our Columbia students (Malawista, to be published) made an incomplete epidemiological study of the native population of Liberia last year and found no example of rheumatoid arthritis in a fairly extensive survey of the native population. There was, however, a large sample—about 15 per cent.—of false positive serologic reactions for rheumatoid arthritis as measured by the F II tanned sheep cell agglutination reaction. In contrast to these observations, the frequency of rheumatoid arthritis in Negro populations in the United States is similar to that seen in white populations. The role played by hereditary factors in this disease is not clear. Apparently, the frequency with which positive serologic reactions are seen in families of patients with rheumatoid-factor-positive rheumatoid arthritis is higher than in the general population, but this does not seem to apply to rheumatoid patients in whom the factor is not demonstrable (Lawrence and Ball, 1958). Most observers have seen instances of families in which the incidence of the disease is high, but these are infrequent and numerous examples are available in which a single case of rheumatoid arthritis appears in a large family.

* Delivered at a meeting held at the Wellcome Foundation, London, on December 5, 1958.

It is no longer fashionable in psychiatric circles to talk about personality patterns, but it has seemed to us after rather extensive observation that the patient with rheumatoid arthritis may be characterized as an individual with deep-seated anxieties which are probably justified by the chronicity and discomfort of the disease process. In summary, the average host may be described as an individual in middle life but with a wide age range, living in a temperate climate, of varied racial extraction, and occasionally with an impressive family history of rheumatoid arthritis.

The course of the disease emphasizes the problems that one must face. Short and others (1957) stressed two types of clinical course: episodic, *i.e.* of less than 6 months duration and sustained. These may merge and an episodic onset is not uncommon. In sustained disease, a remission may occur at any time. This variable life history has been a major factor in the present-day uneasiness regarding therapeutic evaluations. The disease is often progressive with ever-increasing increments of deformity and restriction of function as time passes; indeed, not uncommonly patients followed for 30 years have had no periods of freedom from rheumatoid manifestations.

In a study of the reaction of the host to this disease, the first point of attack should be the tissues involved. The involvement of connective tissues in rheumatoid arthritis had led to its designation as primarily a disease of connective tissue. This may be true, yet one can say that almost every disease involves the connective tissue, including even such a well-established and understood phenomenon as pneumococcal pneumonia, where the primary locus is the connective tissues of the lung. Nevertheless, the varied and widespread participation of connective tissue demands the most serious consideration in a discussion of pathogenesis in rheumatoid arthritis.

May I present, therefore, as a working hypothesis, the suggestion that the primary lesion of rheumatoid arthritis is a vasculitis. Following the vasculitis comes granuloma formation, leading ultimately to scarring with resulting fibrosis. Sokoloff, McCluskey, and Bunim (1953) suggested—on limited number of cases, the authors concede—that the rheumatoid nodule develops from a necrotizing vasculitis in its centre which leads to granuloma formation and eventually to the necrosis seen in the late stages. Furthermore, Sokoloff, Wilens and, Bunim (1951), and Cruickshank (1954) have shown that vasculitis is present to a minor degree in other areas, although, in skeletal muscle, there is little necrosis, and it must be emphasized that the necrotizing character of the arteritis is its important feature. Since the advent of steroids, the appearance of widespread necrotizing vasculitis in rheumatoid arthritis has been increasingly noted (Bevans, Nadell, Demartini, and Ragan, 1954; Sokoloff and Bunim, 1957), although examples of this were seen infrequently before steroids came into use (Southwood, Willkens, and McLendon, 1958). It seems reasonable to suggest that this complication is an augmentation of the minor vasculitis seen in the muscle and of the necrotizing vasculitis which is seen in the genesis of the rheumatoid nodule, but the role of steroids in this development is not clear at this time. Thus, in summary, this is a disease of variable course, often sustained, characterized by chronic granulomatous inflammation with an element of arteritis which, in the early nodule, is clearly necrotizing. The characteristic feature is sustained inflammation, primarily vascular, with the granulomatous and sclerotic elements resulting therefrom.

The relatively frequent occurrence of amyloid in association with rheumatoid arthritis has suggested to some investigators by analogy a hypersensitivity pathogenesis. Experimentally, amyloid may be produced by chronic infection with a viable agent (Gellhorn, Van Dyke, Pyles, and Tupikova, 1946) or by hyperimmunization, with its locus in the connective tissue. Thus it is not unreasonable to infer that, in the absence of a viable agent in rheumatoid arthritis, the appearance of amyloid might by analogy suggest the participation of hypersensitivity in its pathogenesis.

Serum sickness demonstrates the best experimental model of joint inflammation and vasculitis on the basis of hypersensitivity presently available to us. The outstanding difference between this model and human rheumatoid arthritis is that no sustained serum sickness has yet been described in man or in an experimental animal. This applies to the joint inflammation studied (Boots and Swift, 1923) in the 20s as well as to the vasculitis described by Rich (1947) and further studied by Germuth, Flanagan, and Montenegro (1957). In all these models, the lesions appear over a brief period of time and then subside. To account for the sustained nature of rheumatoid arthritis, one must therefore invoke an element of autosensitization.

In most instances, protein hypersensitivity of the serum sickness type is characterized by association with circulating antibody, and, in rheumatoid arthritis, the only evidence we have for a circulating antibody at this time is derived from the rheumatoid factor (Ziff, 1957).

The history of the rheumatoid factor affords an

interesting panorama of medical thought concerning the pathogenesis of rheumatoid arthritis. Cecil, Nicholls, and Stainsby (1929), and Nicholls and Stainsby (1931) introduced the factor when they described the agglutination of haemolytic streptococci in this disease. Because they found that a particular streptococcus was agglutinated by rheumatoid serum, they felt strongly that the disease was an infectious one with this streptococcus as the aetiologic agent. Dawson, Olmstead, and Boots (1932) disproved this hypothesis by showing that the agglutination applied to most Group A haemolytic streptococci as well as to a certain number of pneumococci and staphylococci. The belief remained, nevertheless, that the streptococcus might have something to do with the disease. A technician working in Rose's laboratory—Elizabeth Pearce—was a clinic patient of ours with rheumatoid arthritis. While working on rickettsial pox, she contracted that disease as well. When her serum was set up for complement-fixation studies with the *Rickettsiae*, it was noted that her serum would agglutinate sensitized sheep cells in high titre. Thus, the sensitized sheep cell reaction which had been described by Waaler (1940) was unwittingly resurrected, and not until the phenomenon had been published (Rose, Ragan, Pearce, and Lipman, 1948) did one of the authors recall that she had heard Waaler's original communication at the 2nd International Congress of Microbiology. Heller, Jacobson, Kolodny, and Kammerer (1954) noted that the human gamma globulin would inhibit the sensitized sheep cell reaction, used tanned sheep cells to absorb the gamma globulin, and described the tanned sheep cell F II agglutination reaction. Latex particles (Singer and Plotz, 1956) apparently adsorb gamma globulin as well and afford a much more readily available supply of particulate matter.

Lamont-Havers (1955) showed that two factors were necessary for the development of the streptococcus agglutination—a specific rheumatoid one and a non-specific one which presumably sensitized the suspended streptococci. The implication was that this was an antibody to the streptococcus—a gamma globulin. At about this time, suspicions were expressed (Epstein and Ragan, 1956) that we were dealing with a factor which reacted with gamma globulin in some fashion and the F II precipitin reaction was described (Epstein, Johnson, and Ragan, 1956) which has many of the characteristics of an antigen-antibody reaction. This served to place the phenomenon of the rheumatoid factor on a plane where quantitative immuno-chemical techniques could be employed. Franklin, Holman, Müller-Eberhard, and Kunkel (1957) characterized the factor as a 19S gamma globulin, probably circulating as a soluble complex with a Svedberg constant of 22S which can be dissociated by various means into two components, a 19S (the active factor) and a 7S gamma (Table I). Christian (1958) characterized the reactant gamma globulin in the F II tanned sheep cell reaction and the F II precipitin reaction as an aggregated gamma globulin which can be produced artificially by heating. When antibody combines with antigen, the antibody is in an aggregated form. Christian's findings indicate that the gamma globulin which reacts with the rheumatoid factor is also in an aggregated form. In this reaction, therefore, gamma globulin is in a physical state similar to that in which it exists when in combination with antigen, as in immune precipitates. His observations apply to the F II tanned sheep cell and precipitin reactions where antigen is not available. In all other reactions where rheumatoid factor combines with gamma globulin, the globulin is combined with antigen before reacting with rheumatoid factor in the usual antigen-antibody complex : sensitized sheep cell, brucella-antibrucella (Foz and Batalla, 1955), human Rh-anti Rh (Waller and Vaughan, 1956), eggwhite-anti-eggwhite (Vaughan, 1956). The latex-fixation technique is the exception and it is assumed that the charge on the latex may cause aggregation when the gamma globulin becomes adsorbed to the particle. The rheumatoid factor can combine with its own naturally existent circulating aggregated 7S gamma—*in vitro* at 4° C.—as a spontaneous precipitate. The possibility of an auto-immune reaction thus becomes a tenable hypothesis.

TABLE I

RHEUMATOID FACTOR

Rheumatoid Factor		Gamma Globulin	Reaction
19 S	+	Non-aggregated gamma globulin ($S_{20}=7$)	→ Soluble complex ($S_{20}=22$)
19 S	+	Aggregated gamma globulin ($S_{20}=>7$)	→ Insoluble complex (precipitate)
19 S	+	Aggregated gamma globulin ($S_{20}=>7$) coated on tanned sheep erythrocytes	→ F II agglutination
19 S	+	Aggregated gamma globulin as antibody in combination with antigen*	→ Agglutination of particles or adsorption of rheumatoid factor on immune complexes

* Systems studied:
(1) Sheep cells—Rabbit amboceptor
(2) Brucella—Antibrucella serum
(3) Human Rh cell—Anti Rh serum
(4) Eggwhite—Anti-eggwhite serum

It is entertaining to recall that during the period of popularity of the infectious aetiology of rheumatoid arthritis, the rheumatoid factor appeared in the guise of an infectious agent. At present, when hypersensitivity is the vogue, the factor may be invoked to support the role of hypersensitivity with an element of autosensitization. If speculation is at all proper, it might be suggested that the rheumatoid factor represents an antibody to an antibody when the latter exists as an antigen-antibody complex. It possesses many of the characteristics of an antibody, but it is species non-specific. It will react with rabbit gamma globulin in combination with sheep cell antigen as well as with bovine, guinea-pig, or human gamma globulin. This definite species non-specificity leads immuno-chemists to doubt that the factor is a true antibody. It should be noted, however, that in human thyroiditis, the sensitization is not species specific, for these patients have antibodies to thyroid of other species, as well as antibodies to human thyroid (Rose and Witebsky, 1955).

Vaughan and Harris (1958) injected rheumatoid factor of high titre into volunteers with no significant results. The disappearance curve of the factor in these volunteers, as measured by titration in an appropriate agglutinating system, was similar to that observed with other types of homologous serum protein, indicating that the recipient did not treat the factor as a foreign protein. Recently Christian has injected aggregated gamma globulin in large amounts intramuscularly into two patients with severe rheumatoid arthritis, again without clinical or serological effect. When administered to the guinea-pig intravenously, aggregated gamma globulin removes complement.

Many investigators have noted that individuals with agammaglobulinaemia may develop joint findings resembling those of rheumatoid arthritis (Janeway, Apt, and Gitlin, 1953). In rebuttal, it may be mentioned that these patients do not develop the rheumatoid factor and that a few of the patients with this syndrome have the capacity to make fixed tissue antibody. Thus, to date, the attractive concept that the rheumatoid factor may represent a circulating antibody, thereby providing a tool for desensitization of the patient with rheumatoid arthritis, has not borne fruit. Moreover, transmission of the factor to volunteers does not produce the disease; in the so-called false positive individuals, the factor is present without the disease, as is also the case in some unaffected siblings of patients with rheumatoid factor-positive rheumatoid arthritis. It remains, however, our only definite link between the clinical disease, rheumatoid arthritis, and the nebulous hypothesis of autosensitization. If it develops that the factor plays no role in this mechanism, we are deprived of a most hopeful lead. We must then search for an antigen in a disease which offers no animal experimental model, a disease involving the arterial walls and probably the whole connective tissue.

The absence of definitive evidence of an infectious agent and the sustained nature of the disease strongly suggest an element of autosensitization. Thyroiditis (Rose and Witebsky, 1955), and allergic encephalitis (Kabat, Wolf, and Bezer, 1947) are prototypes of such a mechanism. The need is to find the antigen. If this be the fixed tissue or delayed type of hypersensitivity, the presence of a circulating antibody would be unlikely. There would, therefore, be no readily available technique by which to identify the antigen such as is possible when a circulating antibody is present. But there is evidence which points to a localization of the process in the connective tissue and possibly in the blood vessel wall. Zweifach (1954), however, suggested that while the first visible lesion is in the blood vessel wall, the actual primary insult may be in the loose areolar tissue close to but not necessarily directly contiguous to the blood vessel wall. This is mentioned solely to underscore the point that the first visible lesion may not be the locus of the proposed antigen. It must also be emphasized that microbial agents, such as rickettsiae and even viruses (Jones, Doll, and Bryans, 1957) have been shown to produce a disseminated vasculitis. Hypersensitivity provides only one of several mechanisms for the development of this pattern.

Search for a pure antigen involves us directly in the chemical complexity of connective tissues. Study of the chemical composition of the connective tissue has long lagged behind the chemistry of other body constituents. Its importance has been recognized, but the technical difficulties are enormous, a fact easily apparent as one works in close proximity to Karl Meyer's laboratory. In citing Karl Meyer for a Lasker Award in 1956, it was noted that he and F. O. Schmitt had opened an area which had been largely overlooked. When I first entered this field in 1941, hyaluronic acid had only recently been described. The isolation of identical material in vitreous humour (Meyer and Palmer, 1936), synovial fluid (Meyer, Smyth, and Dawson, 1938), and in the capsule of Group A haemolytic streptococci (Kendall, Heidelberger, and Dawson, 1937) led to a unifying and simplifying concept of the nature of connective tissue.

Subsequent events have not borne out this hope. With each succeeding year, the number of new

polysaccharides, their relationship to tissue proteins, the native physical state of the materials, their state of polymerization, of binding with weak or strong bonds, has forced one to suspect that the possible relationship of these materials to disease states as we know them will be established in our time only by chance. In order to prove that a disease is due to hypersensitivity, some chemical purity of the antigen is necessary, though not to the degree required by the immuno-chemist working with gel diffusion techniques. The material must be somewhat refined and those who have run a Waring blendor making a brei of tendon as a first step toward isolation of one of the chondroitin sulphates quickly realize, at the end of the first step in isolation, that the product has little relationship to the native material. If the antigen requires subtle forces such as hydrogen bonds or Wanderval's forces to develop its antigenic potency, isolation of a pure antigen by the techniques presently available seems unlikely. The known components of the connective tissue are outlined in Table II. The greatest chemical purity obtained so far is in the acid mucopolysaccharides. Their distribution as shown in Table II demonstrates the complexity of the problem at a glance.

In the chemical isolation of connective tissue components, two major difficulties present themselves. The first lies in the fact that isolation procedures practically always modify the native state of the material, either by decreasing the chain length of the polysaccharides so that they are less polymerized in the isolated than in the native state or by breaking certain weak bonds between a polysaccharide and a protein thus possibly changing the biological significance of the material. The second difficulty is due to the ease with which small amounts of material can be overlooked. A classic example of this is the discovery of keratosulphate in various tissues by Meyer, Hoffman, and Linker (1958). The complexity of the chemistry of these materials is overwhelming, and they require extremely special knowledge and a great deal of hard work for their isolation. Undoubtedly further research will increase our overall knowledge of connective tissue, but I must confess that in the past 15 years the augmentation of this overall knowledge has added few concepts as regards the pathogenesis of rheumatoid arthritis. There is no easy road to the understanding either of the composition of the connective tissue or of its relationship to the problem of rheumatoid arthritis.

All materials which have now been isolated in pure form have not yet been proved antigenic. The work of Hill and Cruickshank (1953) in the antigenicity of basement membrane and reticulin and of Scott (1957) on the differentiation of the two are certainly landmarks in this field. The antigenicity described by Hill, and later defined by Scott, as localizing in the reticular structures of the body, could possibly be related to an antigen to reticulin itself but at present these experiments cannot be construed as demonstrating the antigenicity of reticulin. Though the chemical structure of this material is only vaguely understood at this time,

TABLE II

COMPONENTS OF CONNECTIVE TISSUE

Blood and Lymph	Lipid	Pigment	Scleroproteins			Polysaccharides
			Elastin	Reticulin	Collagens	
Proteins Lipids Polysaccharides Mucoids Sialic acid	Fatty tissue Fat depots	Water soluble Lipid soluble	Pigments	Lipid Carbohydrate	Tropocollagen Procollagen Acid soluble Neutral salt soluble Insoluble carbohydrate	Neutral Acid

ACID MUCOPOLYSACCHARIDES OF CONNECTIVE TISSUE—DISTRIBUTION

Heparitin Sulphate	Kerato-sulphate	Hyaluronate	Chondroitin	Chondroitin Sulphate		
				A	B	C
Aorta All blood vessels (?)	Cornea Nucleus pulposus Bone Adult cartilage	Synovial fluid Umbilical cord Skin Ligaments Aorta Tendon Almost all connective tissue	Cornea	Cartilage Bone Aorta Cornea	Skin Tendon Heart valves Aorta Yellow ligaments	Nucleus pulposus Cartilage Bone Tendon Embryonal tissue

there is undoubtedly a carbohydrate closely associated with it. In the human synovium, used by Scott to prepare his antigen, there may have been at least fifty or sixty different chemical substances. It is possible that this same number of substances may be in the material which is stained by fluorescent antibody although they were still distinct from the others present in glomeruli.

None of the mixtures or fractions of connective tissue, either autologous or homologous, which have been injected into the usual laboratory animal, has produced anything resembling rheumatoid arthritis. These materials have been injected by various routes employing the usual techniques for augmenting responses such as alum precipitate and Freund's adjuvant.

If the particles of material are large, granulomatous lesions in the lungs have been produced—probably a foreign body reaction at the site where the particles are screened out in the pulmonary capillary bed. If the particles are small, the animals have shown nothing. Various isolated materials from Karl Meyer's laboratory, including hyaluronate and chondroitin A, B, and C, as well as aggregated gamma globulin, have failed to produce a skin reaction in patients with rheumatoid arthritis which differed in any way from that seen in controls. Let me emphasize again that the materials which have so far been made available to us have been non-reactive in patients with rheumatoid arthritis. We have no alternative but to continue such studies, but it is disturbing to realize that the presently available isolation techniques may destroy important linkages and that, moreover, we may be dealing with a type of hypersensitivity in which there is no skin response.

Lastly, we may be investigating a mechanism which requires man for its development. If this assumption be true, further advances will continue to be difficult, for most of the great forward steps in medicine have been assisted immeasurably by the employment of experimental animals. One experimental model which would be of inestimable value in this field would be an animal which would develop a self-perpetuating reaction of hypersensitivity that involved the connective tissue or the blood vessel walls. This we do not now have. A model which deserves further study is the parabiotic rat which, rarely, develops in one partner a relatively sustained vasculitis, arthritis, and haemolytic anaemia (Hall and Hall, 1951).

In contrast to the rapidly growing knowledge of liver cells and the glomeruli, we know relatively little about fibroblasts. These cells are dispersed, one cannot readily study them in slices or in a brei, and a method has not yet been developed for isolating fibroblasts as is done by the differential centrifugation of glomeruli. The life history of the fibroblast—its origin and its half-life—is the subject of considerable dispute, as is its potential for transforming itself into other types of cell under appropriate stimuli. Tissue culture methods have been used in an attempt to solve some of these problems, and they have proved difficult, though we have been able to show that fibroblasts in culture produce hyaluronic acid and a chondroitin sulphate (Grossfeld, Meyer, Godman, and Linker, 1957). One main source of disappointment has been the dedifferentiation of fibroblasts from various sources on prolonged culture. Only recently, methods have been developed which permit accurate quantitation of polysaccharide production in relation to growth as measured by DNA content. These will provide us with a tool for studying the metabolism of the fibroblast and may possibly help in exploring the antigenicity of the cell itself and of the materials it produces when grown in a relatively simple medium free of blood vessels and circulating materials.

Suggestions have been made that microbial hypersensitivity may play a part in the development of rheumatoid arthritis. Evidence presented in favour of this is indirect and difficult to interpret. The role of this mechanism may be important but cannot be evaluated at this time.

As a last possible speculation, the observation of Beiser, Erlanger, Agate and Lieberman (in the press), concerning the antigenicity of albumin conjugated steroids and the inhibition of the specific precipitin reaction by a particular steroid, suggests the possibility that the adrenal steroids may in themselves be the offending antigen in some instances, and that the anti-inflammatory effect of the 11-oxysteroids may perhaps represent an excess of antigen preventing the combination of antigen and antibody in the tissues.

In summary, failure to discover a circulating antibody would discourage the hope of an early solution to the pathogenesis of rheumatoid arthritis. A continuing characterization of the chemical and physical composition of the connective tissue is necessary coupled with a willingness to determine whether newly discovered compounds have an antigenic role. If a circulating antibody does exist, the most readily available one is the rheumatoid factor, which resides in the fraction containing known antibodies, appears in the circulation as a soluble complex, and reacts with autologous material. Until the possible pathogenic role of this factor is thoroughly and completely disproved, it provides the only support for the implication of

hypersensitivity in the pathogenesis of rheumatoid arthritis. If its role is disproved, we face a long, hard struggle which can be solved in the foreseeable future only through great luck with a dash of serendipity.

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RESORPTION OF INTRACUTANEOUSLY INJECTED CONGO RED*

BY

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Since the introduction of the intravenous Congo red test by Bennhold (1923), a number of writers have recorded observations on the intracutaneous injection of Congo red dye.

Philpott and Freshman (1936) and Nomland (1936) observed intense and prolonged staining of cutaneous amyloid deposits in patients following the local injection of Congo red solution.

Laine, Holopainen, and Mäkinen (1956) noted that Congo red solution injected into the apparently healthy skin of a group of rheumatoid arthritics disappeared more slowly than in control subjects. Shannon, Fessel, and Bywaters (1957) confirmed Laine's findings in a group of juvenile arthritics and observed that the delay in fading was most marked in the younger age groups. They noted that another dye, Evans' blue, failed to show this difference in fading.

No cause is known for this apparent dermal avidity for Congo red in patients with rheumatoid arthritis, but Shannon and others suggest a relationship to the increased tissue retention of intravenously injected Congo red demonstrated in these subjects by Dixon, Ramcharan, and Ropes (1955). If this were so, then the skin of rheumatoid patients with secondary amyloidosis might be expected to show this delay in fading rate, perhaps to a more marked degree.

The purpose of this paper is to report a study of the fading rate of intracutaneously injected Congo red in a group of mainly adult patients with rheumatoid arthritis and to compare these with a small group of patients with amyloidosis. The results are compared with those in a control group.

Methods

The method was similar to that used by Laine and others (1956) and modified by Shannon and others (1957), with the exception that aqueous 1 per cent. Congo red was used instead of a saline solution, as it was found that a deposit occurred if the saline solution was allowed to stand for 24 to 48 hours.

0·1 ml. aqueous 1 per cent. Congo red solution (Savory and Moore) was injected into the medial aspect of the forearm or upper arm. A red area 1 to 3 cm. in diameter was formed, which at 24 hours was compared with a series of standards labelled 1 to 8, produced by dyeing Whatman No. 1 filter paper in serial dilutions of Congo red solution 0·25 to 0·00195 per cent. A reading was then taken, and after an interval of 7 days a second reading was made. An arbitrary index indicating "Fading Rate", hereafter designated F.R., was calculated by dividing the number of degrees of fading by the interval in days. The higher the F.R. the greater the rate of fading of the Congo red.

In the presence of jaundice or other skin pigmentation, the red tint of the Congo red was altered, but the intensity of the skin coloration could usually be matched without difficulty.

During the course of the investigation a number of factors thought possibly to influence the F.R. were investigated.

Site of Injection.—The fading rates in the upper arm and forearm were compared by simultaneous injection of the solution. The mean of tests performed in ten patients showed an F.R. of 0·6 for the upper arm and 0·56 for the forearm. These figures do not differ significantly.

In a few patients the effect of altering the volume of dye injected was observed by comparing the F.R. of 0·1 ml. and 0·2 ml. injected into opposite arms. This did not seem to influence the results.

Repeatability.—Serial tests were performed on a number of patients and controls and close agreement was found in subjects with normal and abnormal F.Rs.

Comparison of Aqueous and Saline Solutions of Congo Red.—To determine if the solvent for the Congo red influenced the F.R., the aqueous solution was compared with a saline preparation. One per cent. aqueous Congo red was mixed with an appropriate volume of 20 per cent. sodium chloride solution to give a final concentration of 0·9 per cent. This was allowed to stand for

* Paper read at a clinical meeting of the Heberden Society on December 5, 1958.

48 hours and centrifuged to remove any deposit. The resulting solution was compared colorimetrically with the 1 per cent. aqueous solution and the latter diluted with pyrogen-free distilled water to render the concentration equal. The solution was then autoclaved.

Thirteen patients were tested by observing the F.R. of the aqueous and saline solutions in opposite arms. The mean fading rate for the aqueous solution was 0·68 and for the saline solution of Congo red 0·65. Similar results were obtained when the saline solution was injected immediately after preparation. Clearly then the use of a saline solution does not influence the results significantly.

Subjects

The rheumatoid arthritis subjects were mainly in-patients in the Hammersmith Hospital; a small number of the younger patients were seen at the Rheumatism Research Unit of the Canadian Red Cross Memorial Hospital, Taplow.

The control group of subjects included healthy members of the staff, and other in-patients with diseases other than rheumatoid arthritis (*e.g.* hypertensive and ischaemic heart disease, and gastro-intestinal and respiratory diseases) of all age groups.

Results

The F.Rs. in both rheumatoid and non-rheumatoid subjects are shown in Table I with subdivision into sex and age groups, together with the standard deviations for each group.

Rheumatoid Group.— The group of 66 rheumatoid arthritics included 45 females and 21 males. Their ages varied between 6½ and 85 years (mean 46 yrs in males; 47 yrs in females). The mean F.R. for the females was 0·61 and for the males 0·62 (±S.E. 0·04 (S.D. 0·21)). Although the numbers in the sub-groups are small, there does not seem to be a significant variation with age; however, two of thirteen subjects below the age of 20 years had F.Rs. of less than 0·3, while only two of 53 subjects above the age of 20 years had abnormal F.Rs.

If only patients with a positive Rose-Waaler (D.A.T.) test are considered, the mean F.R. was 0·63 (± S.E. 0·04 (S.D. 0·16)). Similarly, in a group of patients described as having active disease with erythrocyte sedimentation rates above 20 mm./hr, the F.R. was 0·61.

Effects of Steroid Hormones.—As a number of these rheumatoid patients were receiving steroid hormones, the influence of these steroids was observed in a group of nine patients with rheumatoid arthritis and two with other diseases; the F.R. was determined both before and during the course of treatment with steroid hormones.

The group included subjects with both normal and abnormal F.Rs. and the dose of hormone used varied between 50 and 150 mg. cortisone and 10 and 30 mg. prednisolone daily. The mean F.R. without steroid treatment was 0·60 and with the hormone 0·55. This difference was not significant.

In another group of five patients, hydrocortisone acetate was added to the Congo red solution before injection, in a dose of approximately 10 mg./ml., *i.e.* 1 mg. in each injected dose. Once again no significant difference in F.R. was observed from that of the aqueous solution in the opposite arm.

Control Group.—The non-rheumatoid control group was composed of 96 subjects, 51 female and

TABLE I

FADING RATES IN RHEUMATOID AND NON-RHEUMATOID SUBJECTS, BY AGE AND SEX

Series	Non-Rheumatoid						Rheumatoid					
Sex	Males			Females			Males			Females		
Age Group (yrs)	No.	Mean Age (yrs)	Mean F.R.	No.	Mean Age (yrs)	Mean F.R.	No.	Mean Age (yrs)	Mean F.R.	No.	Mean Age (yrs)	Mean F.R.
0–20	0			2	17·5	0·30	3	11	0·80	10	13	0·54
21–40	12	34	0·64	10	31	0·42	5	36	0·60	3	28	0·62
41–60	20	54	0·63	26	51	0·57	10	47	0·60	17	49	0·67
Over 60	13	65	0·57	13	68	0·62	3	67	0·54	15	68	0·59
Total	45	51	0·59	51	50	0·54	21	46	0·62	45	47·5	0·61

Fading Rate	Total Non-Rheumatoid			Total Rheumatoid		
	Mean F.R.	S.E. of Mean	Standard Deviation	Mean F.R.	S.E. of Mean	Standard Deviation
	0·56	±0·026	0·25	0·61	±0·026	0·21

45 male, with ages varying from 17 to 72 years. The fading index in the female group was 0·54 and that in the male group 0·59 (± S.E. 0·04 (S.D. 0·25)). The differences between these means and those of the rheumatoid group were not significant ($p = 0·6$ for males and $p = 0·2$ for females).

When all the results are plotted as a scatter diagram (Fig. 1, opposite) of F.R. against age, the lack of correlation with age is clearly illustrated, and it is apparent that most results lie above the 0·3 level of F.R. This level was found to be two standard deviations below the total mean F.R. of the whole group, and levels at or below 0·3 are therefore considered abnormal. If the 28 patients with an F.R. of 0·3 or less are considered, a certain grouping of diagnoses is observed (Table II).

This Table shows that the rheumatoid patients did not contribute materially to the abnormal group, except in those cases complicated by amyloidosis. In fact, only two uncomplicated adult rheumatoid arthritis patients had an F.R. of 0·3 or less. These groups will therefore be considered separately (Table III).

Lupus Erythematosus.—The group included eight patients with systemic disease and one with chronic discoid disease of long duration. All showed a F.R. of 0·3 or less, and in two intense staining persisted for 9 and 7 months respectively until death. The mean F.R. in this group was 0·13 (± S.E. 0·04 (S.D. 0·10)), a highly significant difference from the rheumatoid group and the control group as a whole ($p = <0·001$).

All the patients with systemic disease were receiving steroid hormones at the time of the test. At autopsy two patients had dye persisting at the injection site and frozen sections of this area showed

TABLE II

DIAGNOSIS IN 28 PATIENTS WITH FADING RATES OF 0·3 OR LESS

Diagnosis		No. of Patients Tested	No. with Results of 0·3 or Less
Lupus Erythematosus		8	8
Amyloidosis	Secondary to rheumatoid arthritis	5	3
	Secondary to tuberculosis and sepsis	2	2
Jaundice		16	10
Rheumatoid Arthritis	Juvenile (aged under 20)	13	2 (1 with amyloid)
	Adult	53	4 (2 with amyloid, 1 suspected amyloid)
Anasarca and Polyserositis*		1	1
Leukaemia with Cryoglobulins		1	1

* This patient had multiple serositis and oedema without renal disease. Four other cases of nephrotic syndrome had normal fading rates

TABLE III

FADING RATES IN PATIENTS WITH LUPUS ERYTHEMATOSUS, AMYLOIDOSIS, AND JAUNDICE

Disease	Number of Cases		Mean Age (yrs)	Number of Cases with F.R. of 0·3 or Less	Mean F.R.	Standard Error of Mean	Standard Deviation
	Male	Female					
Lupus Erythematosus	1	7	38	8	0·13	0·04	0·10
Amyloidosis	4	3	40	5	0·24	0·08	0·21
Jaundice	8	8	51	10	0·31	0·06	0·24

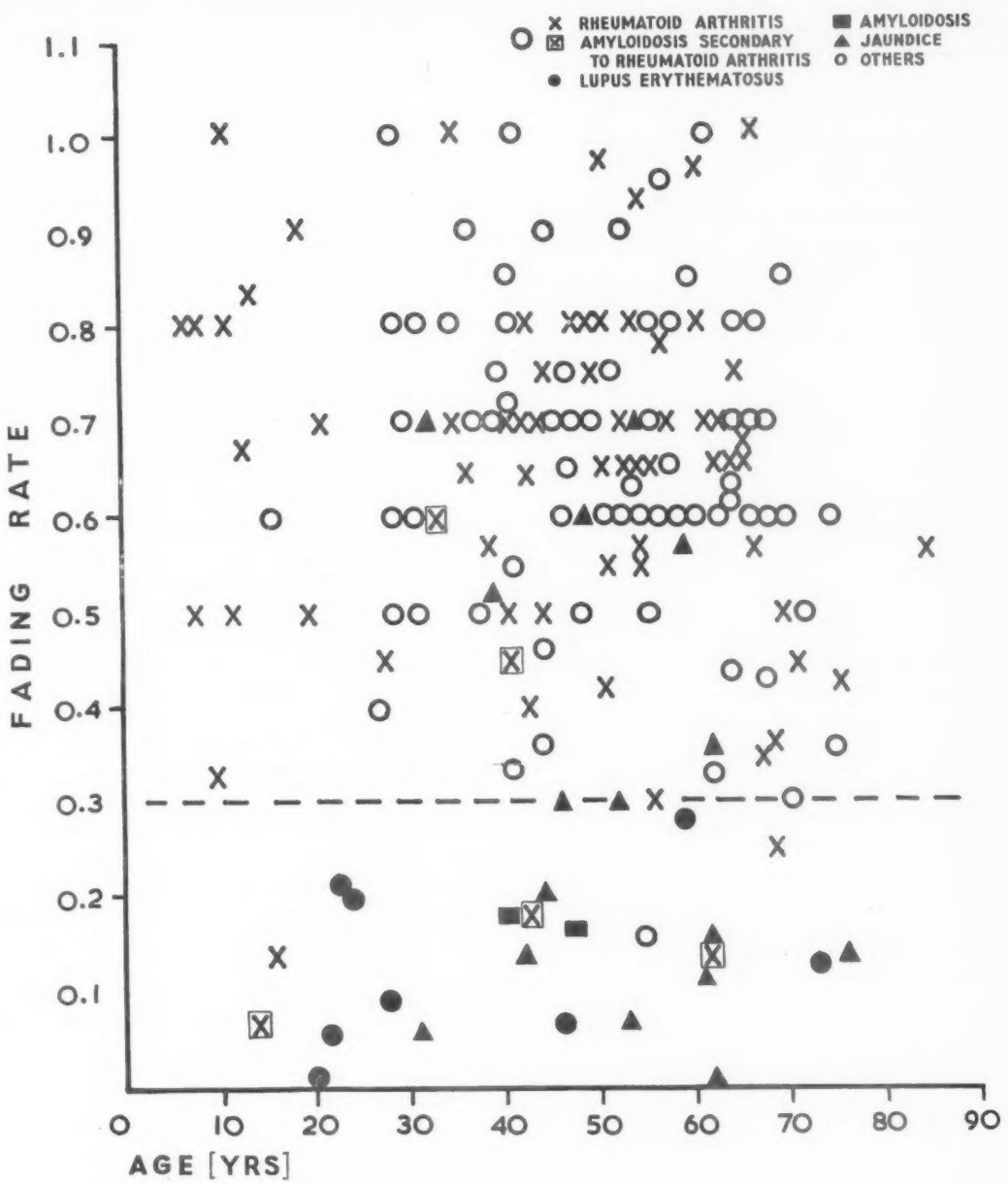

Fig. 1.—Scatter diagram of F.R. according to age and diagnosis.

the dye to be present as minute, possibly intracellular, particles. No staining of collagen fibres was seen. Sections stained with haematoxylin and eosin revealed no histological abnormality.

Amyloidosis.—Seven patients were tested; in five the amyloid was secondary to rheumatoid arthritis, in one to pulmonary tuberculosis, and in the other to post-operative bronchopleural fistula.

Three of the five rheumatoid subjects with amyloidosis and the two non-rheumatoid cases of amyloidosis had F.Rs. of less than 0·3.

The mean F.R. for this group was 0·24 (± S.E. 0·08 (S.D. 0·21)), statistically different from that of the control group ($p = <0·001$).

In all but one patient, in whom the diagnosis was confirmed at autopsy, intravenous Congo red tests were carried out. In Fig. 2 these are plotted against the F.R.; although the numbers are few there is a tendency for a high Congo red clearance to be associated with a slow rate of skin fading.

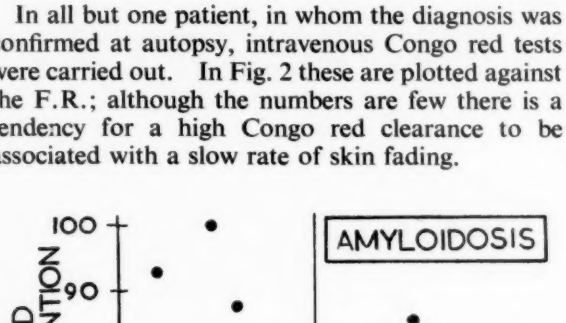

Fig. 2.—F.R. and Congo red retention in cases of amyloidosis.

In each of these patients the area of skin injected appeared normal, and in one histological examination of the injection site at autopsy failed to reveal evidence of local amyloidosis.

Jaundice.—Sixteen subjects were examined. The results are given in Fig. 3 and Table IV.

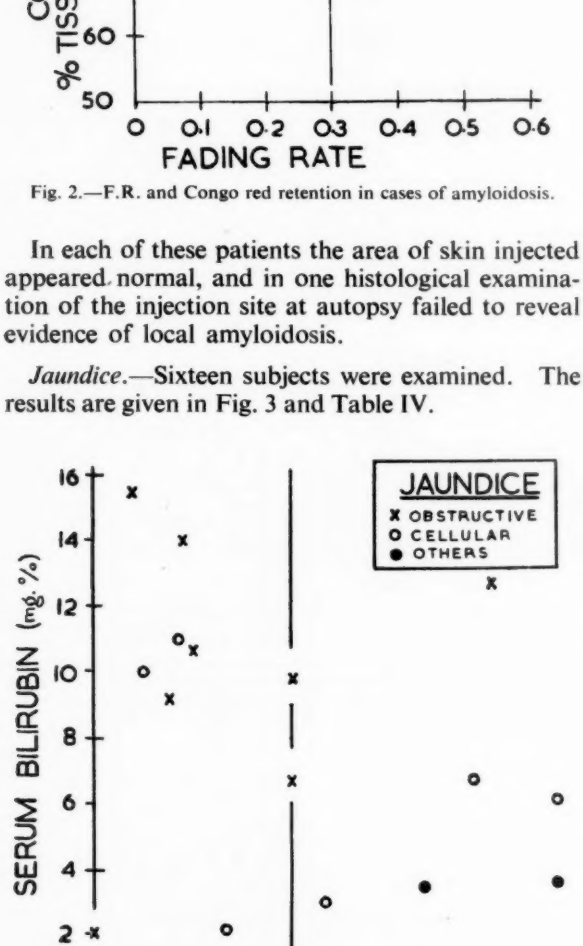

Fig. 3 —F.R. and serum bilirubin in cases of jaundice.

TABLE IV

RESULTS IN PATIENTS WITH JAUNDICE

Type of Jaundice	No. of Cases	No. of Cases with F.R. of 0·3 or Less
Obstructive	8	7
Cellular	6	3
Haemolytic	1	0
Biliary Cirrhosis ..	1	0

There was no correlation between plasma bilirubin, alkaline phosphatase, or flocculation tests and the F.R.

In one patient with obstructive jaundice, the F.R. returned to normal, after surgical relief of the obstruction, before the serum bilirubin had fallen to normal.

Although once again the numbers are small, slow rates of fading were seen most frequently in patients with obstructive jaundice.

An attempt was made to assess the effect of bile salts on the F.R. by incorporating sodium taurocholate into the Congo red solution used for injection. The salt was added in a concentration of 1 mg. to 0·1 ml. 1 per cent. Congo red. This solution was compared with the aqueous 1 per cent. Congo red in six patients, and no difference in F.R. was observed.

As these abnormal groups were discovered in the main rheumatoid and non-rheumatoid groups it seemed wise to reconsider the mean F.R. of both these groups again, after excluding the patients with lupus, amyloidosis, and jaundice, who are given in Table III. These results are shown in Table V, in which the mean values for the rheumatoid and non-rheumatoid groups are in even closer agreement. Despite the minor differences in technique it will be noted that the mean F.Rs. in the present series closely correspond with those in Shannon's control group, *i.e.* 0·67 (S.D. 0·24).

TABLE V

RESULTS AFTER EXCLUDING PATIENTS FROM TABLE III

Male and Female	Mean F.R.	Standard Error of Mean	Standard Deviation
Non-Rheumatoid	0·65	0·022	0·19
Rheumatoid ..	0·65	0·022	0·17

Discussion

The results presented here are in contrast with those reported by Laine and others (1956) whose group of 55 rheumatoid arthritis patients were not defined as regards age and disease activity. The work of Shannon and others (1957), however,

suggests that young rheumatoid arthritics resorb Congo red at a considerably slower rate than control children in the same age group. The few young patients in this series failed to show a consistently slow F.R. In older patients we have shown no correlation between age and fading rate either in the rheumatoid arthritic group or in the control group, both of which showed similar rates of fading.

The abnormal results in the lupus, amyloid, and jaundiced patients are of interest, but the mechanism of their production is difficult to determine. No common factor could be found in the groups of patients which gave these abnormal results.

Not all the patients with abnormal F.Rs. were treated with steroids, and no significant alteration occurred when patients were treated with cortisone or its analogues.

It is possible that the reduction in skin, blood, and lymphatic flow in seriously ill patients could be responsible for the delay in resorption in some of these patients. However, only a small number of the patients with abnormal fading rates were seriously ill at the time of testing, while normal results were seen in dying patients in the control group.

Abnormalities of serum proteins are common in patients with lupus, amyloidosis, and hepatocellular jaundice. Electrophoresis of their sera frequently shows a low serum albumin level and raised gamma globulin levels. Since Congo red is transported in the blood in combination with albumin, the lowered level of serum albumin might be responsible for the decreased rate of resorption from the skin. However, since four patients with the nephrotic syndrome and low serum albumin levels had normal F.Rs., this phenomenon may be related more closely to altered tissue "plasma protein" (Humphrey, Neuberger, and Perkins, 1957).

Clearly, further investigation is required to establish the factors producing the abnormality of fading rate in these groups of patients. Histological examination of skin from the injection site in patients with abnormal fading rates may establish accurately the site of deposition of the Congo red.

Summary

The vital staining of the skin with intracutaneously injected Congo red solution was investigated in 162 rheumatoid and non-rheumatoid subjects. No difference was found in the fading rates between adult rheumatoid arthritis patients and a control group of non-rheumatoid patients.

The activity of the rheumatoid disease did not influence the fading rate and no correlation could be found with age in either group.

Abnormally slow resorption was found in each of eight subjects with lupus erythematosus and gross delay was observed in two.

Patients with amyloidosis showed a slow fading rate in the absence of histological abnormality of the skin.

Jaundice delayed resorption in a high proportion of subjects: this was most noticeable in obstructive jaundice.

No common factor could be found to account for the production of these abnormal results.

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DISCUSSION

PROF. BYWATERS: I do not think there is much to add to this paper. There are very striking differences in patients in the rate of fading, and this is an attempt to give a quantitative assessment to the phenomenon, to try and account for the differences. We do not feel that we have got very far with this problem. The differences may possibly be due to the raised plasma globulins of these patients which are reflected in the tissue proteins, but that is merely speculation and we should be grateful for suggestions.

DR. C. RAGAN (*New York*): Could you not show to which protein the Congo red is bound by electrophoresis with this test; and which is the protein which is separated?

DR. A. ST. J. DIXON (*Hammersmith*): It is not possible to do an electrophoresis of a mixture of dye and serum, as the Congo red binds to the paper and does not move.

DR. J. BALL (*Manchester*): I think it may be worth mentioning a little experiment which Dr. Dixon and I tried out shortly after reading a paper about the Congo red retention test for amyloid which suggested that retention was sometimes seen in rheumatoid patients when amyloidosis had been unsuspected. At the time we wondered whether there were tissue components other than amyloid tissue which bound the dye. We took out some rheumatoid nodules which we thought might retain Congo red, and when some of the fibrinoid was put into the aqueous solution of Congo red one could see staining. We added the Congo red to serum in concentrations which we imagined would obtain in the ordinary Congo red test, and under those circumstances there was no take-up by the tissue at all; it was thought that the serum was preferentially binding the Congo red.

It may be that intradermal staining is due to the formation of an insoluble dye-protein complex which is taken up by the connective tissue cells locally.

PROF. BYWATERS: Laine, Holopainen, and Mäkinen (1956) studied the rate of disappearance from the skin of intradermally-injected aqueous Congo red solution. They observed a slower rate of fading in subjects with rheumatoid arthritis than in a control group. Shannon, Fessel, and Bywaters (1957), using a saline solution of Congo red, demonstrated delayed fading in juvenile rheumatoid arthritis, most marked in the younger age groups, and possibly related to the increased tissue retention of intravenously injected Congo red, demonstrated by Dixon, Ramcharan, and Ropes (1955). This paper reports the fading rates in 66 subjects with rheumatoid arthritis (mainly adults) compared with those in 96 controls including healthy subjects and hospital in-patients with miscellaneous diseases.

0·1 ml. aqueous Congo red solution was injected intradermally into the arm and the stained area compared at 24 hrs and at 7 days with a set of standard colours prepared from serial dilutions of Congo red solution. The results were expressed as a fading rate. Analysis of the results failed to show a delayed rate of fading in the adult rheumatoid patients compared with normals. There was no relation to active disease, raised erythrocyte sedimentation rates, or positive Rose-Waaler tests; nor did age or sex influence the fading rate. Abnormally slow fading rates were seen in 28 subjects, of whom only six suffered from rheumatoid arthritis. Of these six, one had suspected and three had proven secondary amyloidosis. Two patients with amyloidosis secondary to other diseases had slow fading rates. Eight patients with lupus erythematosus, seven of whom had systemic disease, all showed delayed fading from apparently healthy skin. Sixteen jaundiced patients were studied and ten were found to have slow fading rates; of these, seven had obstructive jaundice. There was no correlation with serum bilirubin or alkaline phosphatase levels. Some of the subjects with rheumatoid arthritis and all of those with lupus were receiving steroid hormones at the time of testing. To exclude these hormones as a factor in the delayed fading rate, tests were carried out both before and during steroid treatment in nine patients; no significant difference was observed in the fading rates. The incorporation of hydrocortisone or bile pigments into the Congo red solution before injection similarly failed to influence the rate of fading.

No common factor could be found to explain this apparent dermal avidity for Congo red in the three groups of patients, but all three have abnormal serum proteins and perhaps abnormal tissue proteins too in consequence.

Résorption du rouge Congo injecté par voie intradermique

RÉSUMÉ

On étudia chez 162 sujets rhumatisants et non-rhumatisants la coloration vitale de la peau après l'injection intradermique d'une solution de rouge Congo. On n'observa pas de différence entre les vitesses de décoloration chez les rhumatisants arthritiques adultes et chez les témoins non-rhumatisants.

Le degré d'activité de la maladie rhumatismale n'influença pas la vitesse de décoloration et on ne trouva pas de corrélation avec l'âge dans aucun groupe.

Une résorption anormalement lente fut observée chez tous les huit sujets atteints de lupus érythémateux et il y eut un fort délai chez deux d'entre eux.

Les malades atteints d'amyloïdose accusèrent une vitesse de décoloration faible en l'absence de toute anomalie histologique de la peau.

Un ictère ralentissait l'absorption chez un grand nombre de sujets; ceci était particulièrement prononcé dans l'ictère par obstruction.

On ne put trouver aucun facteur commun qui expliquerait comment se produisent ces résultats anormaux.

Resorpción del rojo Congo inyectado por vía intradérmica

SUMARIO

Se estudió en 162 sujetos reumáticos y non-reumáticos la coloración vital de la piel después de inyecciones intradérmicas de una solución de rojo Congo. No se vió diferencia alguna entre las velocidades de descolorimiento en los sujetos adultos con artritis reumatoide y los testigos non-reumáticos.

La actividad de la enfermedad reumática no ejerció influencia alguna sobre la velocidad de descolorimiento y no se encontró una correlación con la edad en ningún grupo.

Se observó una resorpción anormalmente lenta en los ocho casos de lupus eritematoso y en dos de ellos la demora fué considerable.

Los enfermos con amiloidosis acusaron una velocidad de descolorimiento débil en la ausencia de toda anomalía histológica de la piel.

La ictericia demoraba la absorpción en una gran proporción de los casos, particularmente al tratarse de ictericia por obstrucción.

No se encontró ningún factor común que pudiera explicar estos resultados anormales.

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ANKYLOSING SPONDYLITIS IN WOMEN

BY

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In the 12 years since the Rheumatism Clinic was started at Westminster Hospital a special interest has been taken in ankylosing spondylitis, and although male patients have predominated it has become evident that this is an important cause of skeletal pain and disability in women also. Few series describing the condition as it affects women have been published. Tyson, Thompson, and Ragan (1953) reviewed sixty cases observed during the previous 20 years at the combined arthritis clinics of the Presbyterian and New York Hospitals; they noted a rather more frequent involvement of the cervical spine and symphysis pubis in women, and they thought that the course of the arthritis was more benign, but they concluded that on the whole there was little difference in the clinical picture between the sexes. Forestier, Jacqueline, and Rotes-Querol (1956) referred to fifty female patients; they also observed that spinal deformity was less frequently seen and was less severe than in men, but they did not consider that there were enough differences to justify the description of a female form of the disease.

The present report is an analysis of the thirty female patients who have attended the clinic in the past 12 years in whom ankylosing spondylitis has been diagnosed. Several of them have been observed over several years; a full clinical examination has always included a note on the spondylometer reading, and on the chest expansion, as this is reduced at an early stage in the disease (Hart and Maclagan, 1955). Radiographs of the sacro-iliac joints were taken in all cases, and other parts of the skeleton were *x*-rayed when there were clinical indications.

Clinical Features

Sex Incidence.—The ratio has generally been considered to be about 10 men to one woman; in recent years a ratio of nearly 5 to 1 has been reported (Blumberg and Ragan, 1956; Wilkinson and Bywaters, 1958). While the present series of thirty female patients has been observed, however, 315 men have attended the Clinic, giving an incidence of 9·5 women to 100 men. This figure is given only for what it is worth, since it is clear that in any personal series many irrelevant factors affect the sex incidence; in the present instance the proportion of men is almost certainly increased because a large number of the patients were referred from the Armed Services.

Age at Onset.—This ranged from 13 to 34 years (average 22). This resembles the age at onset in men and confirms that ankylosing spondylitis in women as well as in men is primarily a disease of young adults; it is also a clear point of difference from rheumatoid arthritis.

Family History.—Only one patient gave a history of ankylosing spondylitis in a relative, in this case an uncle; two other patients each had a close relative with rheumatoid arthritis. It has not been possible to examine the relatives of patients and no useful comment can be made on hereditary or familial factors.

Site of Onset.—This is shown in Table I. Pains described as affecting the region of the lumbar spine, sacro-iliac joints, and buttocks were not easily differentiated from one another, and are all included under the first heading (eleven patients).

TABLE I

SITE OF INITIAL SYMPTOM IN THIRTY FEMALE PATIENTS

Site	Patients	
	No.	Per cent.
Lumbar spine and gluteal region	11	37
Lumbar spine and chest	7	23
Dorsal spine	3	10
Whole spine	2	7
Coccyx	1	3
Ischial tuberosity	1	3
Hip joint	2	7
Heel	1	3
Peripheral joints	1	3
Iritis	1	3
Total	30	99

Five patients (17 per cent.) had an extra-spinal onset of pain. Low backache with morning stiffness was the commonest presenting symptom, and pain spreading round the chest especially on coughing was noted as an early symptom in five cases.

Symptomatology.—As the condition progressed other sites were frequently involved, and the cervical spine in particular was often affected; nine patients complained of pain here and four showed radiological changes. This was not, however, noted as an initial symptom, although Tyson, Thompson, and Ragan (1953) found it to be the presenting feature in 5 per cent. of their cases. Pains around the shoulder were also common, being reported by seven patients, but only two had persistent stiffness here, and only one had radiological abnormality (consisting of irregularity of the lateral scapular border with osteoporotic areas above and below the glenoid fossa). In one patient persistent pain with localized tenderness of the left iliac crest was a troublesome symptom.

Case 1, a woman who was first seen at the age of 31, had a 9-year history of intermittent pain in the right hip, upper dorsal spine, and around the chest. Examination disclosed a stiff spine (spondylometer 35°, chest expansion ¾ in.), but her posture was good. A course of radiotherapy (skin dose 1,200r to the whole spine except the sacral region) gave relief of symptoms. A pregnancy the following year had little effect on the spondylitis and her delivery was uneventful. Subsequently she complained of pain and tenderness on the left iliac crest which was not eased by analgesics. Radiographs failed to show any abnormality here, but she was given further local radiotherapy to the area with relief which has to date been permanent. In the last 8 years she has had some low back pain and stiffness and occasional points of tenderness in the buttocks and on the ribs, but has been able to lead a normal life and has only needed occasional aspirin or compound codeine tablets.

This illustrates the way in which bony tenderness at sites remote from any joint may be a prominent feature of the symptomatology.

Radiological Changes

For the purpose of comparison the changes in the sacro-iliac joints have been classified into four grades:

I. Ilial sclerosis with or without apparent widening of the joint space; loss of clarity; slight erosions, affecting less than half of one or both sides.
II. More extensive erosions and ilial sclerosis.
III. Partial joint obliteration.
IV. Complete joint obliteration.

Changes in these joints show a very variable rate of progress (see Table II); complete fusion took place in one patient after only 5 years of symptoms, whereas in two other patients only minimal abnormalities were present after 20 years. In one of these last two patients there was extensive paravertebral calcification ("bambooing") in the lumbar spine associated with slight sacro-iliac changes.

TABLE II

EXTENT OF SACRO-ILIAC JOINT INVOLVEMENT COMPARED WITH DURATION OF DISEASE IN THIRTY PATIENTS

Duration of Disease (yrs)		0–4	5–9	10–14	15–19	20 and Over
Grade of Joint Involvement	I	2	2	1	0	2
	II	2	2	1	1	0
	III	1	1	1	0	1
	IV	0	2	6	1	4
Total		5	7	9	2	7

Where fusion is complete the outline of the joint can still be seen as a "ghost" joint, at the upper end of which there is often a denser point of calcification, the "star" sign (Fig. 1, opposite).

Sacro-iliac involvement was present in every case although occasionally the most advanced radiological changes were observed elsewhere, while there were still only early sacro-iliac changes. One such case with minimal sacro-iliac abnormality and extensive lumbar paravertebral calcification has already been mentioned. In another patient the hips were mainly affected.

Case 2, a girl aged 16 years, developed aching and morning stiffness in the hips. The left hip was immobilized with skin traction and she was given antituberculous chemotherapy; 3 years later this hip was surgically arthrodesed. Later the same year, as pain and stiffness in the right hip increased, this was also immobilized by skin traction and she had a further course of chemotherapy. When she was seen at the clinic the following year there were only a few degrees of movement in the right hip. A radiograph of the sacro-iliac joints showed Grade III changes, but a review of the films taken 2 years after the onset of the spondylitis when the hips were radiologically involved showed only minimal Grade I changes.

This case illustrates the difficulty of early diagnosis when bony and arthritic lesions start in the hips or even more peripherally, and not in the more usual sacro-iliac region. Such early hip involvement is

Fig. 1.—Ankylosis of sacro-iliac joints. Note line of "ghost" joints with residual "star" at top of obliterated joint.

not confined to women and has been observed more than once in our male patients; in both sexes bilateral ankylosis occurs rapidly, especially if the patient is immobilized.

The second most common part to be affected radiologically was the lumbar spine, which was affected in twelve patients (Table III).

TABLE III

SITE OF RADIOLOGICAL ABNORMALITY IN THIRTY FEMALE PATIENTS WITH SPONDYLITIS

Site	Cases	
	No.	Per cent.
Sacro-iliac joints	30	100
Lumbar spine	12	40
[Lumbar spine bambooing]	[5]	[17]
Dorsal spine	9	30
Cervical spine	4	13
Hips	2	7
Symphysis pubis	7	23
Ischial tuberosity	3	10
Shoulders	one each	
Sterno-clavicular joints	one each	
Knees	one each	
Hands	one each	
Feet	one each	

The impression was gained that radiological changes outside the sacro-iliac joints were less frequent than in men. Paravertebral calcification also appeared to be less common in this small series, but it could develop within 5 years of the onset of symptoms. In three patients it was extensive and affected the whole spine (Fig. 2, overleaf).

When the costo-vertebral joint was grossly involved, it gave the appearance of a flared rib (Fig. 3, overleaf).

The development of a massive "bridge" of calcification with no history of trauma was watched in one case by serial films, as it arose between the bodies of L3 and L4 over the course of 2 years (Fig. 4, overleaf).

There did not appear to be in this series an unduly frequent involvement of the cervical spine, but lesions of the symphysis pubis were common (Fig. 5, overleaf).

These consisted of erosions, widening, and sclerosis, and were accompanied in two patients by local tenderness. Painful lesions with radiological changes were also observed at sites away

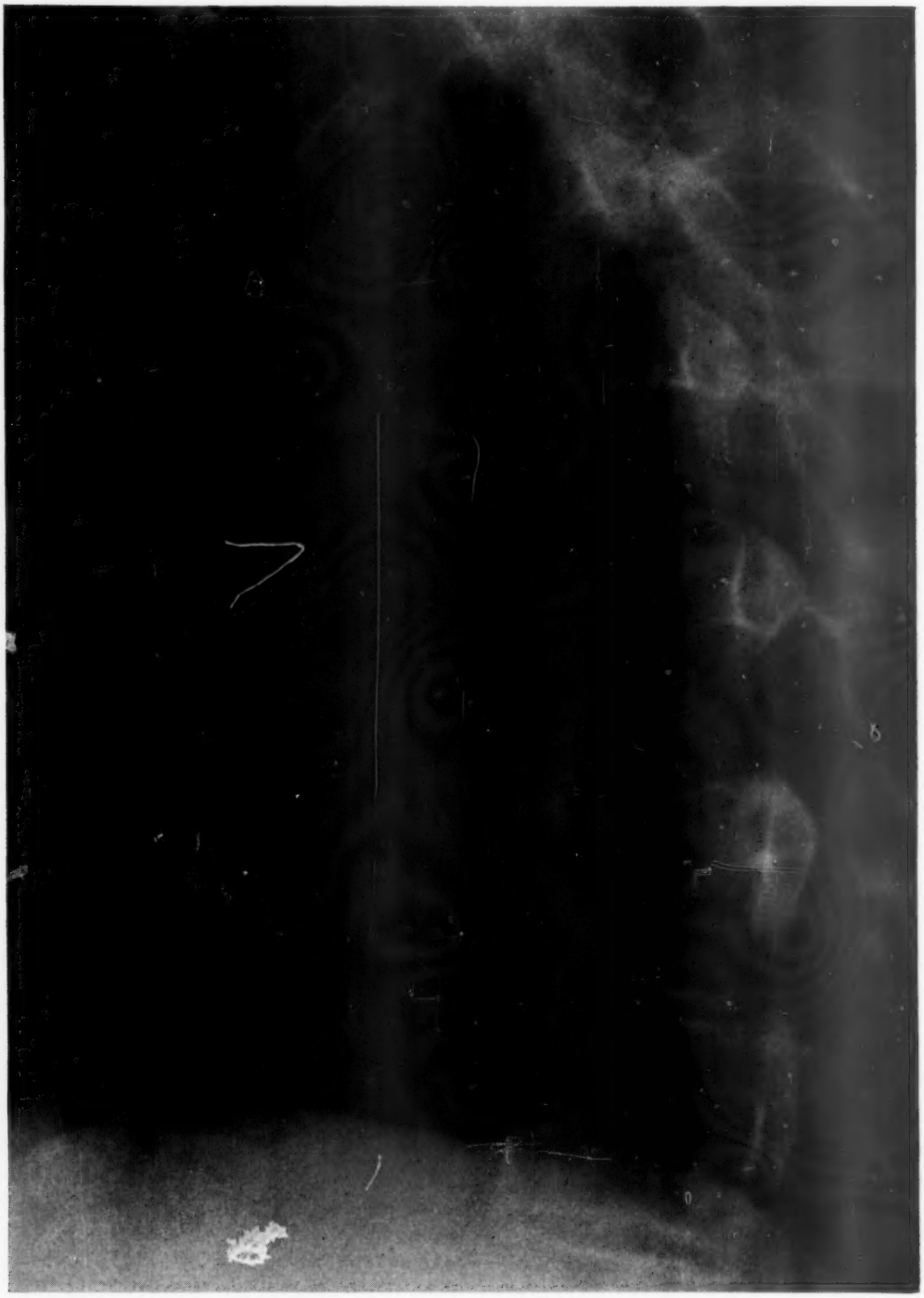

Fig. 2.—Dorsal spine, showing gradual obliteration of anterior margins of disk spaces by paravertebral calcification.

Fig. 3.—"Flared ribs", indicating fusion of rib to vertebral body.

from articular structures; one such patient presented to the orthopaedic department with a persistently painful heel. *X* ray showed a calcanean spur which was porotic when compared with the adjacent bone. A history was then obtained of low backache for 2 years; spinal movement was good (spondylometer 60°), but the chest expansion was only 1½ in. and the erythrocyte sedimentation rate was raised. There were characteristic *x*-ray signs in the sacro-iliac joints, and the symphysis pubis was also affected. This patient developed her first attack of iritis in the following year. In the one patient who had associated psoriasis there were widespread "feathery" changes around the pelvis

(*a*) 1948 (*b*) 1949

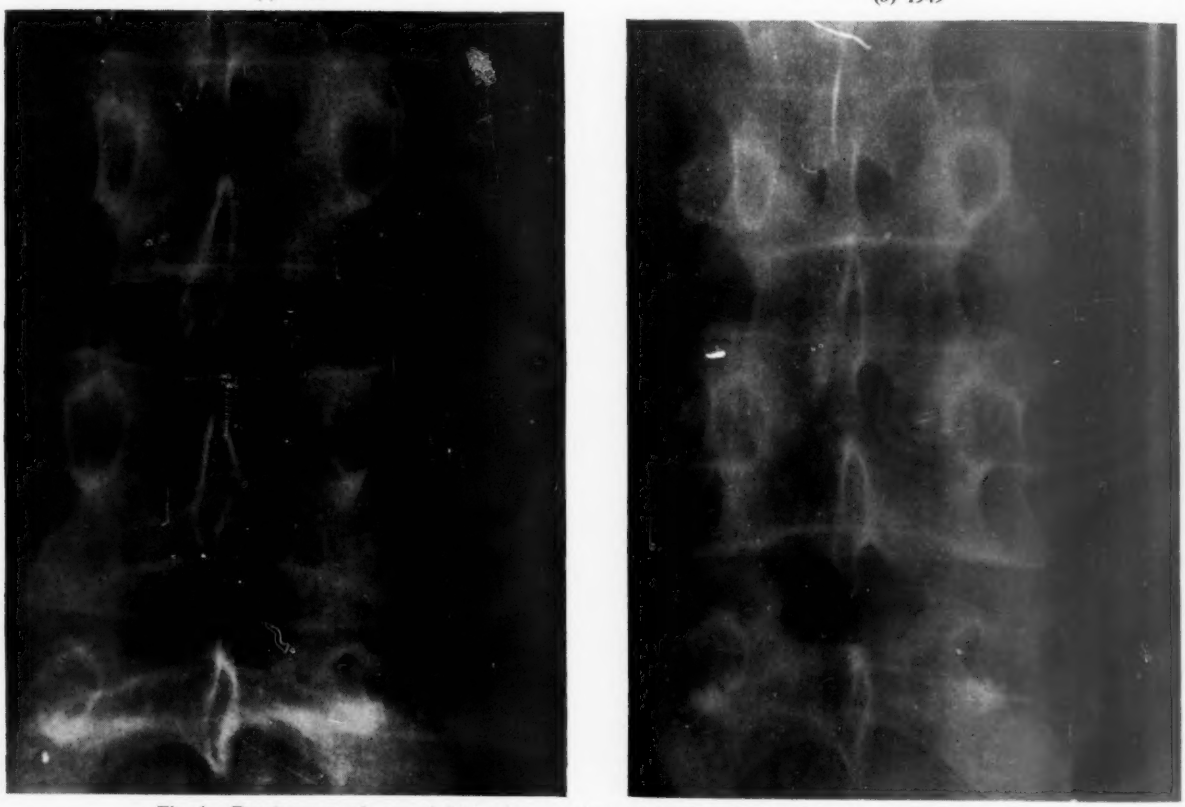

Fig. 4.—Development of coarse bridging between the bodies of Lumbar 3 and 4: 1948, 1949, 1950, 1955.

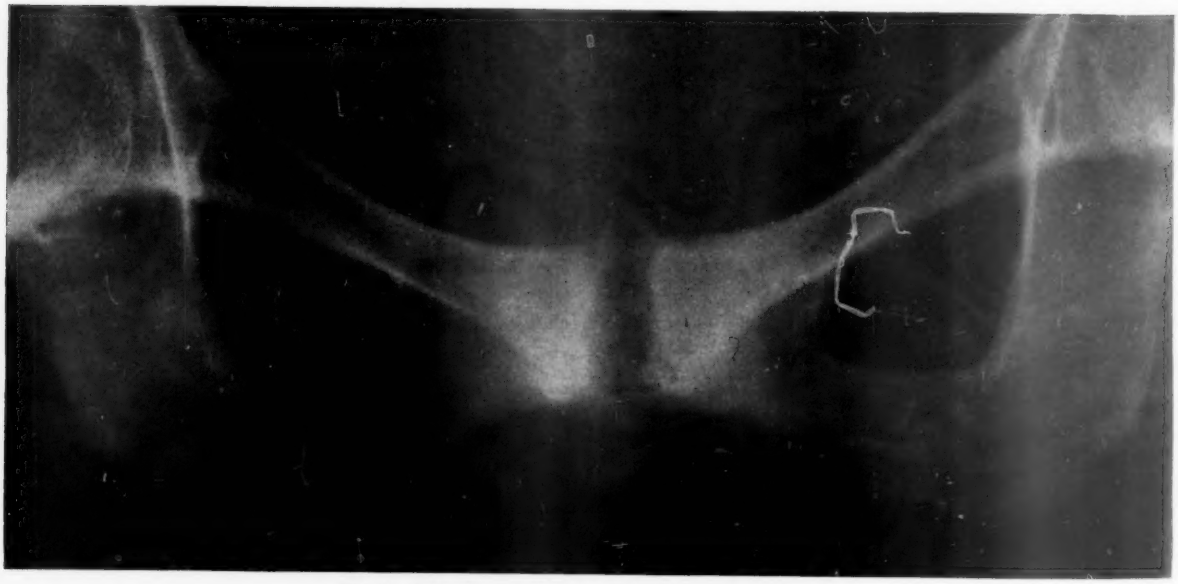

Fig. 5.—Widening, erosion, and sclerosis of symphysis pubis.

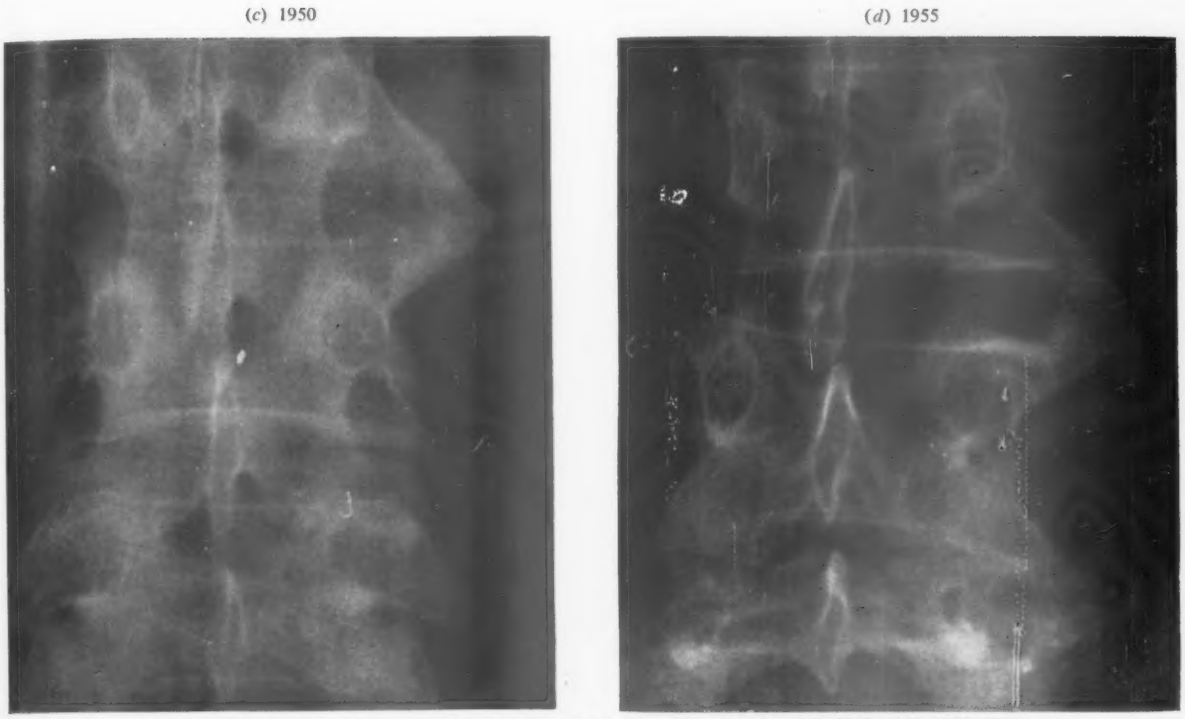

Fig. 4.—Development of coarse bridging between the bodies of Lumbar 3 and 4: 1948, 1949, 1950, 1955.

and extending down on the femora (Fig. 6, overleaf).

Pregnancy

Twenty women out of this series of thirty patients were married and fourteen had had one or more pregnancies. None noticed significant aggravation or improvement in the disease during cyesis. The obstetric management in two of them has been reported in detail elsewhere (Hart, Bell, and Organe, 1951); there were no significant complications in the others. Seven said the symptoms of spondylitis were worse after the pregnancy, but no objective alteration was noted, and there was no apparent increase in the progress of the disease. Two said they were improved after the pregnancy and the other five noted no difference. In view of the importance which pelvic infection is claimed to play in the aetiology of ankylosing spondylitis in men (Romanus, 1953), it is interesting that none of the patients gave any history or had any clinical features suggesting such infection. Two patients had minor menstrual irregularities when the spondylitis was particularly active.

Associated Diseases

Iritis.—This occurred in seven patients. This gives an incidence of 23 per cent., and is similar to that reported by other authors in their combined series of male and female patients (Blumberg and Ragan, 1956; Wilkinson and Bywaters, 1958). In four patients there were multiple attacks; in one the first episode preceded the rheumatic symptoms by 14 years, and it was ultimately the recurrence of the iritis which led to further investigation and the diagnosis of spondylitis.

Other Conditions.—Apart from iritis the following occurred once each: acromegaly, psoriasis, schizophrenia, pulmonary tuberculosis, spinal tuberculosis, and a cauda equina lesion of undetermined aetiology. Eleven patients had dyspeptic symptoms at one time or another; barium meals were thought necessary in only two, and one of these showed a peptic ulcer. There were no cases of valvular or other heart lesions. The patient with psoriasis developed this at the age of 14; spinal symptoms began 18 years later when she was 32, and 11 years after this the peripheral joints became affected. Now, 5 years later, she has typical psoriatic arthropathic changes in both hands and wrists. Apart from this patient, six others had symptoms or signs of involvement of peripheral joints consisting of swelling and tenderness of the hands, knees, and feet.

Fig. 6.—Feathery irregularity of outer surface of pelvis and both trochanters in a patient with psoriasis. There were also typical psoriatic changes in the hands; despite this radiotherapy produced an improvement in spinal symptoms which has lasted since it was given 10 years ago. (By courtesy of Dr. Michael Good.)

Treatment and Course of Disease

Eleven patients had one or more courses of radiotherapy applied to the spine; relief of pain for varying periods was obtained in six. Of fourteen given phenylbutazone, nine considered that it gave very satisfactory relief of both pain and stiffness and found it superior to the usual aspirin preparations. Side-effects from the drug occurred in two patients and were only of a minor nature.

Perhaps the most striking feature is the variable rate at which the spondylitis progresses. It may spread throughout the entire spine and result in the same advanced changes as are seen in men, with the characteristic forward stoop, loss of rib movement, and rigidity of the spine; five patients were affected to this extent. On the other hand it seems that such severe deformity is less likely to develop than in men, and more often than not the ankylosis is restricted to the pelvis even after many years. One such patient was a woman of 27 who had had the characteristic spinal symptoms for 12 years; she had also had five episodes of iritis. When examined she was found to have a reduced chest expansion ($1\frac{3}{4}$ in.), raised erythrocyte sedimentation rate, and partly ankylosed sacro-iliac joints, but she retained good spinal movement (spondylometer 90°) and good posture. Even when spinal fixation and deformity are present, patients are able to lead relatively normal lives with the help of analgesics. The only patients who were at all disabled were the two with hip involvement; the case history of one of these has already been given (Case 2), but in view of the importance of this complication the relevant details about the other are now given.

Case 3, a woman aged 22, when she developed spondylitis while serving in the Forces, had low backache as her initial symptom, and radiographs showed ligamentous calcification. In accordance with the accepted practice of the time she was put to rest in a plaster bed for 16 months. At the completion of this treatment the hips were fused and she needed the help of crutches to walk. When she attended the Clinic for the first time 3 years later her posture was excellent, but radiographs

showed complete bony ankylosis of the sacro-iliac joints and the hips, as well as extensive changes in the spine.

In Cases 2 and 3 it appears in retrospect that treatment by immobilization was largely responsible for the fixation of the hips.

Discussion

From the small series of cases seen and treated in the clinic at Westminster Hospital and other cases seen elsewhere in consultation, it appears that there is no great difference in this disease as it affects women as compared with men, but that it does on the whole seem to be milder and less likely to produce extensive spinal changes, and to be for this reason more likely to be overlooked. Nevertheless, severe spinal changes did occur in five of the thirty cases here analysed. The apparent onset in the hips noted in two of the patients is particularly dangerous, as in the past such cases have been regarded as tuberculous and treated accordingly. Prolonged immobilization is bad therapy for ankylosing spondylitis, as fusion and subsequent crippling occur rapidly; early mobilization under full analgesic cover, with steroid therapy if necessary, is the better and more logical course.

It is of interest that pregnancy and childbirth had relatively little effect on the course of the disease. There was neither the apparent remission so frequently seen in the rheumatoid patient, nor the subsequent relapse. The burden of extra domestic duties sometimes produced symptomatic aggravation after the baby was born, but the actual disease process remained much the same throughout pregnancy and puerperium. The one patient with psoriasis, now under the care of Dr. Michael Good of Aylesbury, may be considered by some workers as falling into a different category and therefore not comparable to the other cases reported. Time will show how many subdivisions of this disease there may be. This patient has been included to show how such a syndrome can change over the course of the years to another form, and also how *x*-ray therapy applied to an atypical case still appears to have produced a lasting remission in the spinal symptoms while the condition progressed in psoriatic form at the periphery.

Finally, it is painfully apparent, on looking through the case histories of these patients in the past, that those who were not diagnosed early, and therefore did not receive the mistaken immobilization therapy, did better than the others. The only really crippled patients in the series had both been treated by prolonged immobilization. Swaim (1939) emphasized this point in Boston 20 years ago, but it still seems necessary to underline his warning and draw attention again to this danger.

Summary

Some clinical and radiological features of thirty female patients with ankylosing spondylitis are described. This disease appears to run a milder course in women than in men, but a very variable rate of development is noted. Radiological abnormalities in the symphysis pubis were frequently seen. Bilateral lesions of the hip joints developed rapidly in two patients, and were the cause of severe disability; both had been treated by immobilization and this is regarded as having been responsible for the subsequent fixation of these joints. Pregnancy and childbirth had little effect on the course of the disease. The value of phenylbutazone for the relief of symptoms is stressed.

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Spondylarthrite ankylosante chez la femme

RÉSUMÉ

On décrit quelques caractères cliniques et radiologiques de la spondylarthrite ankylosante chez trente femmes. Cette maladie semble suivre une évolution plus benigne chez la femme que chez l'homme, mais on note une vitesse de développement très variable. On nota des anomalies radiologiques fréquentes de la symphyse pubienne. Des lésions bilatérales de l'articulation de la hanche apparurent rapidement chez deux malades, causant une grave incapacité; les deux cas avaient été traités par l'immobilisation, à laquelle on attribue la fixation subséquente de cette articulation. L'effet de la grossesse et des couches sur l'évolution de la maladie fut minime. On souligne l'importance de la phénylbutazone dans le soulagement symptomatique.

Espondílartritis anquilosante en mujeres

SUMARIO

Se describen ciertos caracteres clínicos y radiológicos de la espondílartritis anquilosante en treinta enfermas. Esta enfermedad parece seguir una evolución más benigna en la mujer que en el hombre, pero la velocidad del desarrollo es muy variable. Anomalías radiológicas de la sínfisis púbica fueron frecuentes. Lesiones bilaterales de la articulación de la cadera aparecieron rápidamente en dos enfermas, causando incapacidad grave; ambos casos habían sido tratados con inmovilización, a lo que se atribuye la fijación consiguiente de esta articulación. La preñez y el parto tuvieron poco efecto sobre la evolución de la enfermedad. Se subraya la importancia de la fenilbutazona en el alivio sintomático.

Ann. rheum. Dis. (1959), **18**, 24.

SIGNIFICANCE OF THE WAALER-ROSE TEST, STREPTOCOCCAL AGGLUTINATION, AND ANTISTREPTOLYSIN TITRE IN THE PROGNOSIS OF RHEUMATOID ARTHRITIS

BY

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When the clinical picture of rheumatoid arthritis was defined by Garrod (1859) and practically the same syndrome was termed "rheumatisme articulaire chronique progressif" by Charcot (1874), these terms were used to designate a chronic arthritis, progressing unfavourably and resulting in some degree of permanent disability. Only in the last few decades has it become known that in some cases of rheumatoid arthritis there is complete recovery within a few months. Short and Bauer (1948) have pointed out that cases progressing favourably are by no means as rare as is commonly supposed.

In Anglo-Saxon countries cases progressing favourably are included in the rheumatoid arthritis group, whereas in France such cases are variously termed "rheumatisme articulaire subaigu", "rhumatisme articulaire subaigu curable", or "polyarthrite subaigue", and the term "polyarthrite chronique évolutive" is used exclusively for the types progressing unfavourably. Hence the terms rheumatoid arthritis and "polyarthrite chronique évolutive" are not synonymous, a point which is too often forgotten.

According to de Sèze and Ryckewaert (1954), 25 per cent. of patients suffering from "polyarthrite chronique évolutive" become complete invalids, and the remainder are partly able to continue their work, though about half of the latter suffer severe limitation of activity.

The usual prognosis in cases of rheumatoid arthritis is that 25 per cent. of patients recover, 25 per cent. are incapacitated, and the remaining 50 per cent. show improvement but do not recover completely. Short and Bauer (1948), however, believed that in many cases of rheumatoid arthritis the prognosis is more favourable than is commonly supposed, chiefly depending upon the duration of the disease at the time of the first examination. When the duration of the disease was less than 12 months, remission increased to 37 per cent. Steinbrocker (1946) found that 90 per cent. of the cases of acute rheumatoid arthritis recovered, the only therapy being general medical treatment.

So far it has not proved possible to predict the course of the disease in early cases. A gradual onset with symmetrical involvement of fingerjoints has always been regarded with suspicion. Egelius, Hävermark, and Jonsson (1949) investigated the case histories of 200 patients suffering from advanced rheumatoid arthritis and noted this classical beginning in 37·5 per cent. Sclater (1943) noticed, in a group of 388 patients, an onset in the finger joints in 38 per cent. of female patients and in 26 per cent. of male patients; no attention was paid, however, to symmetrical involvement. The literature does not yield any information about the percentage of cases in which the disease started in the finger joints but developed favourably and resulted in recovery within a few months.

The relation of serological reactions to the prognosis of rheumatoid arthritis has been subjected to various investigations. Kellgren (1952) believed that a positive Waaler-Rose test was characteristic for cases of rheumatoid arthritis which were progressing unfavourably. Ball (1952) found the test positive in 55 per cent. of patients with pronounced *x*-ray changes, and in only 21 per cent. of patients with normal *x*-ray findings.

Present Investigations

Material.—Data were collected from 141 patients in the initial stage of the disease. A diagnosis of rheumatoid arthritis was made when several joints showed inflammatory symptoms, pain, swelling, and functional disorder. Only a few patients showed monarthritis, or great pain in the hands and feet only at the time of the first examination, and in them swelling of other joints soon became apparent. Some patients suffered from disturbances of the locomotor system, extremely painful larger joints,

and a significant increase in the erythrocyte sedimentation rate, conforming with the description of "pseudo-polyarthrite rhizomélique" (Forestier and Certonciny, 1953).

Cases presenting difficulties of differentiation from rheumatic fever have not been included. Most patients felt quite well, and complaints of fatigue were by no means as frequent as is stated in many publications. Brief case histories of the patients are given in the thesis of one of us (Otten, 1958).

The patients were divided into two groups:

(A) Duration of disease at time of first examination 1-3 months (106 patients).

(B) Duration of disease at time of first examination 4-6 months (35 patients).

Method.—Antistreptolysin titre, streptococcal agglutination, and the Waaler-Rose test were performed at the time of the first examination and repeated once or several times subsequently. The technique was the same as that used by Otten and Boerma (1954), but in the last year of observation the Waaler-Rose test was performed with sensitized human O cells instead of with sheep red blood cells (Boerma, 1955; Meijer and Boerma, 1958).

A titre of 1 : 16 is considered positive in the Waaler-Rose test. Positive streptococcal agglutinations refer to L and O agglutination with titres of 1 : 40 or more, no value being attached to a positive titre of only one of these reactions.

Treatment.—Salicylate or amino pyrine was given first, and if no influence upon the disease was observed chrysotherapy was instituted. 32 of the 141 patients were clinically treated in this way during the first year.

Results

Group A

Of the 106 patients in this group, 29 had been ill for 1 month at the time of the first examination, 42 for 2 months, and 35 for 3 months. All 106 patients were observed for at least 1 year, 78 for 2 years, 40 for 3 years, and some for as long as 5 years.

In general the disease had had a gradual beginning, and complaints of fatigue or general malaise were rare.

Sex Differences.—We observed that the initial stage of rheumatoid arthritis was seen nearly as frequently in men as in women, *i.e.* in 48 males and 58 females. It was usually stated that rheumatoid arthritis is much more frequent in women, the ratio being about 2 or 3 to one.

At the end of the first year, 46 patients of the 106 in the series had joint involvement, at the end of the second year 34, and at the end of the third year 22 (Table I). Amongst these patients with continuing joint involvement, in whom the disease might be said to have become chronic, the proportion of women to men increased as time went on. Of the 46 patients under observation who had joint involvement at the end of the first year, 27 were women and nineteen were men; of the 34 patients at the end of the second year, 23 were women and eleven were men; of the 22 patients at the end of the third year, sixteen were women and only six were men.

We may conclude, therefore, that initial attacks of rheumatoid arthritis occur with practically the same frequency in both sexes, but that the chronic form is more often found in women.

TABLE I

RELATIONSHIP OF JOINT INVOLVEMENT TO WAALER-ROSE TEST IN 106 PATIENTS (GROUP A) IN 3 YEARS FOLLOW-UP

Waaler-Rose Test	Joint Involvement									
	Present at Initial Examination	At End of First Year			At End of Second Year			At End of Third Year		
		Present	Absent	Total	Present	Absent	Total	Present	Absent	Total
Positive ..	37	26	11	37	17	4	30	9	1	17
					3	6		3	4	
Negative ..	69	20	49	69	14	0	48	10	0	23
					0	34		0	13	
Total Patients	106	46	60	106	34	44	78	22	18	40

Table I shows that 26 of the 37 sero-positive patients still had joint involvement at the end of the first year; of 21 who were still under observation at the end of the second year 4 had recovered; and of 10 still under observation at the end of the third year 1 had recovered. The other eleven of the original 37 sero-positive patients had recovered by the end of the first year, but three of them had relapsed by the end of the second year, and three still had joint involvement by the end of the third year. The developments in the group of 69 sero-negative patients is set out in the same way, and shows a steady decline in joint involvement and no relapses.

Waaler-Rose Test.—37 of the 106 patients (35 per cent.) had a positive Waaler-Rose test within 3 months of onset of the disease. No difference was attributable to sex. The test proved to be very stable; once it was positive there might be minor fluctuations, but it was exceptional for it to become negative. Even in cases of complete remission for as long as 5 years the test remained positive.

Because a large number of the patients in whom the Waaler-Rose test was negative recovered, there was an increase in the percentage of sero-positive patients with joint involvement from 35 per cent. in the initial stage to 57 per cent. at the end of the first year of observation, and by the end of the third year this had increased to approximately 80 per cent. In some cases the test became positive in the later stages of the disease. Only a few patients recovered after the first year of observation. More than half of the patients who showed joint involvement and a positive Waaler-Rose test in the third year of observation had already become sero-positive during the first few months of the disease.

Course of the Disease.—Most of the patients recovered within a few months, but the others developed chronic rheumatoid arthritis. The prognosis was much better in patients with a negative Waaler-Rose test than in those with a positive test. The patients were therefore divided into two groups: those with positive Waaler-Rose test at the time of the first examination, and those with a negative test at the time of the first examination.

The term "recovery" is used when joint involvement, both manifest and functional, is no longer apparent, no notice being taken of the erythrocyte sedimentation rate or of subjective complaints, such as vague joint pains or morning stiffness. Table I shows the number of patients with joint involvement at the end of each year of observation.

At the end of the first year of observation, 30 per cent. in the sero-positive group had recovered compared with 71 per cent. in the sero-negative group (57 per cent. of the total). Once recovery had set in, no relapses were observed among the sero-negative patients, whereas relapses did occur among the sero-positive patients. Patients still manifesting joint involvement at the end of the first year seldom recovered; this applies to both sero-positive and sero-negative patients. The entire duration of the disease in patients who recovered during the first year of observation varied from 2 to 14 months (average 7). Although the hope of recovery for patients who still showed joint involvement at the end of the first year was small, no continuous progression was seen, and improvement has been known to occur just as frequently as deterioration in the following years.

Antistreptolysin Titres.—The difference between the percentages of increased antistreptolysin titres in sero-positive patients and healthy persons was not significant, but the sero-negative patients differed significantly from both (Table II). In patients with a negative Waaler-Rose test and an antistreptolysin titre of 300 U/ml. or more, rheumatoid arthritis developed favourably, but not more so than in patients of the same group with a normal or only slightly increased antistreptolysin titre.

TABLE II

ANTISTREPTOLYSIN TITRES IN A GROUP OF HEALTHY CONTROLS AND IN THE PATIENTS WITH POSITIVE AND NEGATIVE WAALER-ROSE TESTS (PER CENT.)

Antistreptolysin Titres (U/ml.)	Healthy Controls	Waaler-Rose Test	
		Positive	Negative
>300	4	8	20
200–300	12	8	19
<200	84	84	61
Total	100	100	100

Streptococcal Agglutination.—Of 37 patients with a positive Waaler-Rose test, 28 showed positive L- and O-agglutination with a titre of 1 : 40 or more. Of the 69 sero-negative patients, only eight had such a titre. The course of the disease in the latter group is shown in Table III.

TABLE III

STREPTOCOCCAL AGGLUTINATION AND THE COURSE OF THE DISEASE IN SERO-NEGATIVE PATIENTS

L- and O-Agglutination	Joint Involvement at End of First Year	
	Present	Absent
Positive	6	2
Negative	14	47

In five of the six patients who showed positive L- and O-agglutination and joint involvement at the end of the first year, the Waaler-Rose test became positive later on. It is clear that the recovery percentage is significantly higher when the L- and O-agglutination is negative, and that these reactions have a prognostic significance.

Arthritis of the Fingerjoints.—This was frequently observed at the time of the first examination. The percentage in the sero-positive group was 81, and in the sero-negative group 58. No notice was taken

of symmetrical involvement. 60 per cent. of the sixty patients who recovered in the first year and 78 per cent. of the 46 patients who failed to recover had manifested involvement of the joints of one or more fingers at the time of the first examination. The prognostic value of involvement of the joints of the fingers is therefore slight.

Group B

The 35 patients in this group (27 females and 8 males) had had the disease at the time of the first examination for from 4 to 6 months. Of thirteen patients with a positive Waaler-Rose test, none recovered in the first year, but of 22 sero-negative patients eleven recovered. That the recovery percentage is lower than in Group A is mainly due to selection, since patients recovering within 4 months were not included in Group B. Increased antistreptolysin titres were again found more frequently in the sero-negative than in the sero-positive group. Arthritis of the joints of the fingers was seen in six of the eleven patients who recovered in the first year.

Discussion

To obtain a better insight into the prognosis of early rheumatoid arthritis clinical and serological examinations were made in the initial stage of the disease and repeated during a period of from 1 to 5 years. A considerable number of patients recovered during the first year of observation: in Group A 57 per cent., and in Group B 31 per cent. This confirms the opinion of Short and Bauer (1948) and of Duthie, Brown, Knox, and Thompson (1957), who state that the prognosis depends upon the duration of the disease at the time of the first examination. Initially the incidence of rheumatoid arthritis was almost equal in both sexes, but it reached the chronic stage more frequently in female patients, and at the end of the third year of observation joint involvement was found in sixteen women, but in only six men.

Involvement of the joints of the fingers proved to be of little prognostic value, since it was observed in the initial stage of the disease in 60 per cent. of the patients who recovered during the first year of observation.

More prognostic value could be attached to the Waaler-Rose and the streptococcal agglutination tests. The recovery percentage was much higher in sero-negative patients with normal agglutination titres, than in those who were sero-positive and had high agglutination titres. In Group A, 70 per cent. of the sero-negative patients and only 30 per cent. of the sero-positive patients recovered. Similar findings were reported by Duthie and others (1957).

After the first year of observation, recovery was rare in both the sero-negative and sero-positive patients; the prognosis thus entirely confirms the description of "polyarthrite chronique évolutive" as put forward by the French clinicians. In Group A, 35 per cent. of the 106 patients were sero-positive when examined for the first time, but 80 per cent. were sero-positive of those observed for 3 years. A positive Waaler-Rose test thus appears to be characteristic of chronic rheumatoid arthritis. Patients with a positive Waaler-Rose test have been known to recover, but relapses are frequent. By improving our methods it might be possible to show that the test is positive in all chronic cases, but it is unlikely, in our opinion, that this will ever be seen in the initial stages, since this disease is not a unity but a syndrome. The French clinicians express this by using the terms "rhumatisme articulaire subaigu", "rhumatisme articulaire subaigu curable", or "polyarthrite subaigu" for the type of disease which progresses favourably.

Positive streptococcal agglutination in sero-negative patients had an unfavourable prognostic significance. These positive agglutinations may probably be attributed to a mechanism similar to that of the Waaler-Rose test, *i.e.* the agglutination of particles sensitized with a globulin. This globulin could be a small quantity of specific antibody against streptococci present in many human sera (Lamont-Havers, 1955). Increased antistreptolysin titres were found with greater frequency in sero-negative patients than in sero-positive patients. The clinical picture in these patients did not resemble that of rheumatic fever, and the prognosis was the same as that in patients with normal antistreptolysin titres. The significance of the increase in titre is not clear. Possibly there is some causal relationship between benign rheumatoid arthritis and streptococcal infections.

Summary

The course of rheumatoid arthritis was followed for 1 to 3 years in 141 patients who were first seen in the initial stage of the disease. In 106 patients the duration of the disease at the time of the first examination was 1 to 3 months (Group A), in 35 patients it was 4 to 6 months (Group B). In the first year of observation, 57 per cent. from Group A and 31 per cent. from Group B recovered.

Initial rheumatoid arthritis was seen with about the same frequency in both sexes, but the chronic form more often in women. The Waaler-Rose test was positive in 35 per cent. of the patients in the

initial stage, in 57 per cent. at the end of the first year of observation, and in 80 per cent. at the end of the third year of observation in patients who still had joint involvement.

In Group A, 71 per cent. of sero-negative patients recovered and only 30 per cent. of sero-positive patients. In Group B, half the sero-negative and none of the sero-positive patients recovered. Positive streptococcal agglutinations had an unfavourable prognostic significance in patients who were sero-negative.

If at the end of the first year of observation joint involvement was still present, recovery was rare, quite apart from the result of the Waaler-Rose test. Increased antistreptolysin titres occurred much more often in the sero-negative group than in the sero-positive group or in healthy persons.

The prognostic significance of arthritic involvement of the joints of the fingers was slight.

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Importance de la réaction de Waaler-Rose, des agglutinations streptococciques et du titre d'antistreptolysine dans le pronostic de l'arthrite rhumatismale

RÉSUMÉ

On étudia l'évolution de l'arthrite rhumatismale pendant 1 à 3 ans chez 141 malades vus pour la première fois à la période de début de la maladie. Chez 106 d'entre eux la maladie était présente depuis 1 à 3 mois (Groupe A) au moment du premier examen et chez 35 d'entre eux depuis 4 à 6 mois (Groupe B). Au cours de la première année d'observation, 57% du groupe A et 31% du groupe B guérirent.

L'arthrite rhumatismale à la période initiale fut également répartie entre les deux sexes, mais la forme chronique fut plus fréquente chez les femmes. La réaction de Waaler-Rose fut positive chez 35% des malades à la période de début, chez 57% à la fin de la première année d'observation et chez 80% à la fin de la troisième année d'observation.

Dans le Groupe A, 71% des malades séro-négatifs et seulement 30% des séro-positifs guérirent. Dans le Groupe B, la moitié des séro-négatifs et aucun des séro-positifs guérirent. Les agglutinations streptococciques positives eurent une importance pronostique peu favorable chez des malades séro-négatifs.

Quand l'atteinte articulaire était encore présente à la fin de la première année d'observation, la guérison était rare, indépendamment du résultat de la réaction de Waaler-Rose. Les titres d'antistreptolysine augmentés se trouvaient beaucoup plus souvent chez les séro-négatifs que chez les séro-positifs ou des sujets sains.

L'importance pronostique de l'implication arthritique des articulations des doigts fut minime.

Importancia de la reacción de Waaler-Rose, de las aglutinaciones estreptocóccicas y del titulo de antiestreptolisina en la prognosis de la artritis reumatoide

SUMARIO

La evolución de la artritis reumatoide fué estudiada durante uno a tres años en 141 enfermos vistos por vez primera en al período inicial de la enfermedad. En 106 de ellos (Grupo A) el comienzo de la enfermedad antedató la primera examinación de uno a tres meses, y en los 35 demás (Grupo B) de cuatro a seis meses. En el curso del primer año de observación, un 57% del Grupo A y un 31% del Grupo B recobraron.

La artritis reumatoide inicial fué observada con igual frecuencia aproximadamente en cada sexo, pero la forma crónica fué más frecuente en las mujeres. La reacción de Waaler-Rose fué positiva en un 35% de los enfermos en el período inicial, en un 57% al cabo del primer año de observación y en un 80% al cabo del tercer año de observación.

En el Grupo A, el 71% de los enfermos sero-negativos y sólo el 30% de los sero-positivos recobraron. En el Grupo B, la mitad de los sero-negativos y ninguno de los sero-positivos recobró. Las aglutinaciones estreptocóccicas positivas tuvieron una importancia pronóstica poco favorable para los enfermos sero-negativos.

Cuando la lesión articular estuvo presente hasta al cabo del primer año de observación, el restablecimiento fué raro, independientemente del resultado de la reacción de Waaler-Rose. Los títulos de antiestreptolisina aumentados se vieron más a menudo en los sujetos sero-negativos que en los sero-positivos o en sujetos sanos.

La importancia pronóstica de la implicación artrítica de las articulaciones de los dedos fué poca.

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INDICATIONS FOR SURGICAL INTERVENTION IN RHEUMATOID ARTHRITIS OF THE WRIST AND HAND

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The problems of prolonged disability and pain in the wrist and hand resulting from rheumatoid arthritis are well known, and the management of this generalized disease is primarily a medical problem. Various open operations on these parts have, however, been devised to relieve pain and improve function; it is the purpose of this paper to re-examine the value of some of these and to clarify the indications for their use.

Material

290 polyarthritic patients have been examined over a 6-year period, 265 of them referred to out-patient departments and 25 seen as in-patients, in the South Manchester area hospitals and at the Devonshire Royal Hospital, Buxton. In all cases, the hands and the wrists were affected, but in only 120 was this the primary reason for hospital attendance.

The patients do not represent a complete cross-section of the total rheumatoid population as they had all been referred to out-patient departments or admitted as in-patients, and the milder forms of arthritis were therefore not included. 71 of these patients were operated on, and the type of operation and sex distribution are shown in Table I. All patients were questioned about hand disabilities whether they were complaining of them or not.

The operations were all performed by the same surgeon, who also assessed the operative results. The assessment was based on the patients' statements, the physical signs, and when possible by comparisons with similar controls or with the same condition in the other hand.

Reasons for Advising Operation

(1) Persistent local pain not permanently improved by conservative treatment for 6 months or more; three main types of pain were found:

(*a*) Metacarpophalangeal joint pain due to subluxation.
(*b*) Pain over the inferior radio-ulnar joint and ulnar side of the wrist.
(*c*) Pain over the front of the wrist and lower forearm due to flexor tenovaginitis.

TABLE I

SURGICAL PROCEDURES USED IN 71 CASES, BY SEX.

Surgical Procedure	No. of Cases	Sex	
		Male	Female
Radiocarpal fusion and excision of lower end ulna ..	5	1	4
Excision of lower end of ulna	14	5	9
Excision of flexor sheath and division of anterior carpal ligament	7	0	7
Metacarpophalangeal arthrodesis	4	0	4
Shortening of first metacarpal	8	1	7
Extensor tendon repair ..	14	2	12
Persistent extensor sheath effusion	2	0	2
Excision of metacarpal heads	12	5	7
Arthroplasty of proximal interphalangeal joints	5	1	4
Total	71	15	56

(2) A major permanent deficiency of grasp for individual needs; four main types of grasp deficiency were found:

(*a*) Defective function in the thumb.
(*b*) Incorrigible deformity of the wrist.
(*c*) Defective finger flexion.
(*d*) Tendon ruptures.

In many patients two or more of these factors co-existed, but usually one was dominant. The general state of the disease was considered, and if the patient was not in the ascending phase of an exacerbation, as judged by the history clinical examination and the erythrocyte sedimentation rate, a local increase of heat and swelling at the operation site was not regarded as a contra-indication to surgery; no generalized "flare-ups" have been seen as an obvious result of operation. Psychological factors

were not troublesome, as those patients whom surgery might have helped, but who were temperamentally resistant to rehabilitation, refused operation.

Operative Methods Employed

(1) Wrist.—In this group 26 operations were performed, all with good results,* and twelve patients were not treated by surgery (Table II).

TABLE II
RESULTS OF 26 OPERATIONS ON WRISTS

Surgical Procedure	Operated	Not Operated	Results in Operated Cases
Radiocarpal fusion and excision lower end of ulna	5	0	All good*
Excision lower end of ulna alone	14	8	All good
Excision of flexor sheath and division of anterior carpal ligament	7	4	All good

(*a*) *Radio-carpal Fusion and Excision of Lower End of Ulna.*—All five patients in this category had fixed flexion deformities of the wrist with bony or tight fibrous ankylosis, and these were corrected by wedge resection and arthrodesis of the radio-carpal joint using the lower end of the ulna as inlay graft material. In all cases the grasp was improved satisfactorily, but rotation improved no more than 20° in any case. A reasonable degree of passive finger range was present beforehand; the absence of this was considered to be a bar to operation, and several patients were not operated on for this reason.

52 patients showed clinical instability of the wrist joint with some pain, but the disability was considered too slight to warrant arthrodesis.

(*b*) *Excision of Lower End of Ulna Alone.*—This was carried out on fourteen wrists, in all of which there was a painful subluxation at the inferior radio-ulnar joint; the results were variable (Table III).

TABLE III
RESULTS OF EXCISION OF ULNA

Average Rotatory Range		Pre-operatively	1 year Post-operatively
Excision of Ulna	1 in.	30°	50°
	2½ in.	30°	90°

* "Good" implies (1) Fusion of bone as a result of operation on the carpus, (2) no loss of grip after operation, (3) subjective impression that the hand was more useful and less painful after operation.

All patients gained good relief of pain, and this was appreciated even if the gain in rotation was slight, as in the six cases in which only 1 in. of the ulna was removed. In the other eight cases in which 2½ in. of the ulna was removed, there was a great increase in the average rotation and no real difference in the small amount of post-operative ulnar deviation which was apparently symptomless.

(*c*) *Excision of Flexor Sheath above the Wrist and Division of Anterior Carpal Ligament.*—This was carried out in seven patients (one hand each) to relieve pain which had lasted for 8 months or more. In five of these patients (of whom two had already been treated by local hydrocortisone injection), there was already a general rheumatoid infection, but in the other two there were no systemic symptoms, and the subacute flexor tenosynovitis was the first indication of the disease, which declared itself 18 and 6 months later respectively. In these two cases the pain was particularly intense, preventing sleep and resisting drugs or splinting. All the tendon sheaths, when exposed at operation, were found to be swollen, opaque, and yellow from their proximal limits distally to the distal margin of the carpal tunnel. In one patient with generalized rheumatoid infection the common palmar sheath in the hand was also slightly opaque. The thickened sheaths were excised, and the anterior carpal ligament completely divided. The pain was relieved immediately and has not recurred.

In four similar untreated patients, observed over periods of 2 to 3 years, the swelling has remained, but the pain though still present can be relieved by analgesic drugs and has become less distressing; the disease in the wrist and the hand has advanced in each case.

(2) Thumb.—Inability to make use of the thumb was found to be one of the worst single disabling factors; two main types of case were seen and twelve operations were performed (Table IV).

TABLE IV
RESULTS IN TWELVE OPERATIONS ON THUMBS

Surgical Procedure	No. of Cases	Results
Metacarpophalangeal arthrodesis	4	All good
Metacarpal shortening for ankylosis	8 (6 Still's Disease)	3 Bad 5 Good (Interposition material used)

(*a*) *Radial Subluxation and Instability at the Metacarpophalangeal Joint with Loss of Thumb : Index Opposition.*—This was treated by arthrodesis of the

metacarpophalangeal joint in four hands with good restoration of the thumb : index opposition. Two patients have since asked for similar operations on the other thumb. The interphalangeal joint was also subluxed in two cases but arthrodesis was not carried out.

(*b*) *Fixed Deformity of the Whole Thumb in Bad Position.*—This was treated in eight patients (one thumb each) of which five were cases of inactive Still's disease. In all these, complete bony fusion had occurred at the wrist in neutral or slight flexion, and at the two distal thumb joints in full extension, the thumb being adducted in five cases and neutral in three. The finger range was limited to about 20° at the metacarpophalangeal joint. The thumb could not be opposed to the stiff index and there was therefore virtually no active grasp in the hand at all.

The operation consisted of resection of the proximal third of the first metacarpal. In the first three patients the results were bad, the shaft reconstituting itself with complete bony re-ankylosis within a year. In the other five patients, absorbable gauze was introduced between the cut bony surfaces, after they had been smeared with bone wax; healing was good and though the initial post-operative range of movement diminished by about 20 per cent. in the first 6 months a satisfactory active pincer effect has remained unchanged in all five for periods ranging from 3½ years to 12 months.

(3) Tendon Lesions.—Twenty hands were affected and fourteen operations were performed (Table V).

TABLE V

RESULTS IN FOURTEEN OPERATIONS ON TENDONS

Tendon Affected	Operated	Not Operated	Results in Operated Cases
Extensor pollicis longus	7	4	Good if repaired by tendon transfer
Extensor digitorum longus	6	2	Bad
Flexor pollicis longus	1	0	Good

(*a*) *Extensor Tendon Ruptures.*—These were seen in nineteen patients (one hand each) with established rheumatoid disease with deformity which had usually come on after some weeks or months. The episodes of pain marking the rupture had been noted by all patients, but had caused relatively little alarm at the time. Thirteen of these tendons were repaired by direct suture or tendon transfer, but the deformity recurred early in eight cases despite 3 weeks' post-operative splintage from the forearm to the proximal phalanx.

The residual deformity in both treated and untreated cases was more troublesome after ruptures of extensor pollicis longus than after rupture of extensor digitorum longus, and the results of tendon transfer were all far better than after direct suture. In one patient, in whom a good technical result was obtained from early suture of extensor digitorum longus, some loss of terminal finger flexion in the ring and little fingers actually decreased the power of grasp.

(*b*) *Flexor Tendon Ruptures.*—One example of flexor pollicis longus rupture in the hand was repaired with a good result, though only 50 per cent. of interphalangeal flexion was regained.

(*c*) *Flexor Tendon Nodules in the Palm.*—These were seen in 41 hands none of which were operated upon. In the 25 cases which could be traced and re-examined, the symptoms had ceased to be disabling within a year or so.

(*d*) *Persistent Extensor Sheath Effusions.*—These were seen in seventeen hands, but were removed in only two, largely because of their size. These two patients were pleased with the cosmetic result, but in one small but significant loss of finger flexion occurred. This operation has not been repeated in any one patient.

(4) Digits.—Seventeen operations were carried out (Table VI).

TABLE VI

RESULTS IN SEVENTEEN OPERATIONS ON DIGITS.

Surgical Procedure	No. of Cases	Results
Excision of metacarpal head ..	12	Good
Interphalangeal arthroplasty ..	5	Bad

(*a*) *Excision of Second and Fifth Metacarpal Heads and Necks.*—This was carried out to relieve pain in twelve hands, all of which showed good results. Four patients requested the same operation on the other hand. Nine patients demonstrated that their grasp was better, although the post-operative metacarpophalangeal flexion range showed only an average increase of 20 per cent. at the most. After this operation the hand is shorter, and the oblique palmar furrow potentially deeper, so that the ulnar three fingers can more efficiently oppose the thenar eminence; this appears to be the reason for the improvement in grasp.

(*b*) *Arthroplasty of Fingers.*—Excision of the proximal interphalangeal joint was carried out in five patients (the middle finger in three and the index

finger in two). In each finger both interphalangeal joints were ankylosed in the straight or hyperextended position. On the operating table it was noticed that in every case flexion at the pseudarthrosis of more than 20° or so produced a pale cyanosis of the finger tip; indeed, one finger had to be amputated for dry gangrene a week after operation, though it was on light traction, and not flexed. After 6 months the results in all the remaining cases were poor, the distal segment subluxing backward, probably through contracture of the extensor mechanism over the back of the finger.

Discussion

Considering this series as a whole, it is clear that open operation has a relatively small part to play in the treatment of the rheumatoid hand and wrist. The pain usually responds to conservative treatment, and many of the inevitable deformities are compatible with good painless function. In the whole series of 290 cases, no voluntary complaints were made over painless metacarpophalangeal subluxation, ulnar deviation of the fingers and hand, dislocation of the extensor tendons, loss of finger extension, or instability of the wrist, and it seems that the presence of these deformities is not, in itself, an indication for operation. When, however, there is a fixed wrist deformity with mobile fingers or a thumb which is either unstable, or because of ankylosis, not opposable, operation is beneficial. In the latter event simple metacarpal shortening should be supplemented by interposed material.

With regard to pain as an indication for surgery: where the level of local pain remains high despite treatment, and sleep is persistently disturbed for many months, pain can and should be relieved by one of the above methods. The results obtained by excision of the flexor sheath and division of the carpal ligament were the most impressive, though it must be uncommon to see the disease presenting initially in this way. In dealing with extensor tendon ruptures the best results were undoubtedly obtained with recent ruptures of the extensor pollicis longus, a wrist extensor being used as a motor; the longer the period that elapsed before repair, the worse the result, and in ruptures of the extensors to the middle, ring, and little fingers which were some weeks old, repair has been unsatisfactory.

No direct correction of intrinsic contracture was carried out in this series, as the interphalangeal joints were already stiff in those cases in which it might have helped. The problem of converting the fixed hyperextension of the fingers into useful flexion is not solved. The answer may lie in earlier division of the lumbrical and interosseous insertions, or in interosseous stripping before joint stiffness is established, and this is being investigated. Nor were any operations performed on the 41 patients with flexor tendon nodules in the palm, as their symptoms had ceased to be troublesome within a year or so in the 25 which could be traced for re-examination.

Summary

A series of 290 patients with rheumatoid arthritis has been reviewed over a period of 6 years, in order to discover how function in the wrist and hand may be improved by surgery. A total of 71 operations was performed.

The indications for surgery are assessed in the light of the results of these operations. It is concluded that these indications are infrequent. They are clear, however, in our present state of knowledge, in certain well-defined cases of persistent pain, weakness of grasp, stiffness, and deformity.

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Indications de l'intervention chirurgicale dans l'arthrite rhumatismale du poignet et de la main

RÉSUMÉ

On étudia pendant 6 ans une série de 290 malades atteints d'arthrite rhumatismale afin de trouver comment peut-on améliorer chirurgicalement la fonction du poignet et de la main. On procéda à 71 opérations en tout.

On détermine les indications chirurgicales à la lumière des résultats de ces opérations. On conclut que ces indications sont rares. Elles sont nettes, cependant, à l'état actuel de nos connaissances, dans certains cas bien définis de douleur persistante, faiblesse de la prise, raideur et déformation.

Indicaciones de la intervención quirúrgica en la artritis reumatoide de la muñeca y de la mano

SUMARIO

Se estudió durante un período de 6 años una serie de 290 enfermos con artritis reumatoide con el fin de descubrir como se puede mejorar quirúrgicamente la función de la muñeca y de la mano. Se efectuaron 71 operaciones en total.

Se determinan las indicaciones quirúrgicas a la luz de los resultados de estas operaciones. Se concluye que estas indicaciones son raras. En el estado actual de nuestros conociminetos hay, sin embargo, indicaciones claras en casos bien definidos de dolor persistente, débil asimento, rigidez y deformación.

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EFFECT OF INTRAMUSCULAR INJECTION OF PITUITARY TISSUE IN RHEUMATOID ARTHRITIS

BY

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Pituitary gland implants from other than an identical twin cannot be expected to function in man, whether the source be man or animal, but may act as a temporary source of hormone because of their ACTH content. The gland also contains other hormones and may be better than ACTH because of the slow absorption of hormone. Favourable results have been reported by Edström (1950) and Edström and Thune (1951). We therefore decided to test the efficacy of pituitary implantation in patients suffering from rheumatoid arthritis, determining the ACTH content of the implant, the clinical changes, and the adrenal response compared with that of ACTH.

Materials and Methods

(1) Technique.—The calf hypophysis was removed under sterile conditions and cleaned 30 to 60 minutes after death. One part of the pituitary was homogenized with physiologic saline and another was cut up into five to six pieces of similar size. The homogenate and the minced tissue were injected intragluteally with 200,000 units penicillin. Ejection of the implant occurred in one case and allergic reaction in none.

(2) ACTH Activity of the Implant.—The ACTH activity of the pituitary homogenate in 0·9 per cent. NaCl solution pH 1·0 was determined in various dilutions by the ascorbic acid depletion test of Sayers, Sayers, and Woodbury (1948) using corresponding dilutions of Cortrophin Z (Organon-OSS) as standard, without the addition of a precipitating agent, as described elsewhere (Forgács and Hajdu, 1956). The calf pituitary homogenate was found to be as active as about one twenty-fifth of its weight of the standard ACTH employed.

(3) Classification of Patients.—This was based on the grades described by Steinbrocker, Traeger, and Batterman (1949), except that Stages I and II were taken together as Group A (capable of full normal joint function or with a slight restriction of motion in one or more joints due to articular pain; osteoporosis; limited subchondral bone destruction; slight joint swelling; moderate muscle atrophy; extra-articular changes such as tendovaginitis, periarthritis, etc.).

Group B patients were those in whom impaired function interfered with normal activity so that they were only partially capable of caring for themselves, and showed subchondral rarefaction or destruction of bone, marked muscle wasting, and extra- and intra-articular changes.

Group C comprised completely helpless patients, confined to bed or chair, with severe *x*-ray destruction, muscle wasting, joint deformity, contractures, subluxations, or ankylosis.

(4) Plan of Study.—Patients were treated as hospital in-patients over a period of about 4 weeks and received the following injections at weekly intervals:

(*i*) 20 I.U. long-acting depot ACTH;
(*ii*) Homogenate and minced pituitary (as described);
(*iii*) Placebo (saline);
(*iv*) Brain tissue homogenate.

The order of the injections was varied.

(5) Evaluation of Clinical Response.—Marked improvement, designated "++" in the Table, signifies decrease of pain and restoration of mobility, slight improvement is designated "+", and no improvement or deterioration is designated "0".

(6) Evaluation of Adrenocorticoid Response.—A marked adrenal response (designated "++")

was defined as a mean urinary 24-hrly output of 17-ketosteroids (by Callow's method—see Hajdu and Forgács, 1954) on the 3 days after the start of treatment more than twice that of the preceding resting output. A slight adrenal response was defined as a mean increased output of at least 50 per cent. of the control level, and no response was defined as less than this.

Results

The results are shown in the Table, which shows that pituitary implant failed to produce any more improvement than that produced by control injection, which in turn was itself inferior to that produced by ACTH. There was little or no adrenal response with any of the three treatments. Clinical response was more marked with each treatment in patients in Group A than in those with further advanced disease (Groups B and C).

Discussion

Hypophysis implants introduced in 1937 (Kylin, 1937) have been claimed to benefit not only various endocrine conditions (Westman, 1941; Westman and Jacobsohn, 1942; Edström and Westman, 1942), but also skin diseases (Kühnau, 1952; Vámos, Szendei, and Márton, 1952), trigeminal neuralgia (Bues, 1952), peptic ulcer (Schubert, 1955), and cancer (Gumrich, 1951; Martyn, Simon, and Vizián, 1957), as well as rheumatoid arthritis (Edström, 1950), mainly after the introduction of ACTH by Hench in the U.S.A. Most of these studies came from Europe at a time when ACTH was not generally available, and although they report favourable results they lack critical value (compare Fellinger and Schmid, 1952, who give an account of 6,000 implantations in 1,400 cases). Thus a controlled study like this becomes a necessity and has shown no difference between the cases on treatment and those on placebo.

Summary

The therapeutic and endocrine efficacy of hypophysis hetero-implantation has been studied in 20 carefully observed patients with rheumatoid arthritis, using as a control saline or brain tissue implantations. The results were compared with the response to 20 I.U. ACTH. ACTH produced clinical improvement, but this was seen in only a few of those treated with pituitary implant and paralleled the number of improvements seen in those treated by placebo or control. Hypophysis implantation seems to be no better than placebo therapy.

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TABLE

CLINICAL AND ADRENAL CORTICAL RESPONSES TO DIFFERENT TREATMENTS IN THE THREE STAGES OF THE DISEASE

Group	Case No.	Response to 20 I.U. ACTH		Response to Pituitary Implantation		Response to Brain Implantation or Placebo	
		Clinical	Adrenal	Clinical	Adrenal	Clinical	Adrenal
A	1	++	0	+	0	+	0
	2	++	0	+	++	+	0
	3	+	0	+	0	+	+
	4	++	0	+	0	+	++
B	5	++	0	+	0	0	0
	6	0	0	0	0	0	0
	7	++	++	+	+	0	0
	8	++	0	0	0	0	++
C	9	0	0	0	0	+	+
	10	++	0	+	0	0	0
	11	++	0	0	0	0	0
	12	0	0	0	0	0	++
	13	+	+	0	0	0	0
	14	0	++	0	0	0	0
	15	++	++	0	0	0	0

Effet de l'injection intramusculaire de tissu pituitaire sur l'arthrite rhumatismale

RÉSUMÉ

On étudia l'efficacité thérapeutique et endocrinienne des greffes hétérogènes d'hypophyse sur 20 malades atteints d'arthrite rhumatismale et soigneusement observés, l'eau physiologique et des greffes de tissu cérebral servant de substances-témoins. On compara les résultats à ceux obtenus avec 20 unités internationales d'ACTH. Cette hormone produisit une amélioration clinique qui ne se manifesta que chez quelques malades traités par la greffe pituitaire et chez un nombre correspondant de ceux traités par les substances-témoins. Il apparaît donc qu'une greffe pituitaire n'a aucun avantage sur une substance-témoin.

Efecto de la inyección intramuscular de tejido pituitario sobre la artritis reumatoide

SUMARIO

Se estudió la eficacia terapéutica y endocrina de heteroinjertos de hipófisis sobre 20 enfermos con artritis reumatoide, cuidadosamente observados. El suero fisiológico e injertos de tejido cerebral sirvieron como substancias de control. Se compararon los resultados a los obtenidos con 20 unidades internacionales de ACTH. El tipo de mejoría obtenido con la ACTH se vió tan sólo en pocos casos tratados con el injerto pituitario y otros pocos tratados con las substancias de control. Se concluye que un injerto pituitario no tiene ventaja alguna sobre substancias de control.

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REITER'S DISEASE IN THE FEMALE

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An increasing amount of interest is being shown in Reiter's disease and it is now recognized that the condition is commoner than was at one time believed. In many cases the complete triple syndrome does not occur, or is not recognized, as the ocular and genital components may be symptomless and escape detection unless specially looked for. The disease may be associated either with bacillary dysentery, non-specific diarrhoea, or a venereally acquired urethritis. These forms pursue a virtually identical clinical course and have been called the "dysenteric" and "venereal" syndrome by Harkness (1950a). A curious feature is that the dysenteric syndrome is apparently very rare in Great Britain (Corner, 1950) though it is commonly reported on the continent of Europe (Marche, 1954; Bourel, 1954; Paronen, 1948). Conversely, the "venereal" syndrome appears to be rare in Europe. All authorities agree that the "venereal" syndrome rarely affects the female, indeed some have gone so far as to deny its occurrence in women (Storm-Mathisen, 1946; Lofgren, 1946; Twiss and Douglas, 1946; Vallee, 1946). The existence of the dysenteric syndrome in women was noted, however, in the mid-19th century by Huette (1869).

Zewi (1947), in a paper dealing with the ophthalmological complications of Reiter's disease, described six cases in females. Young and McEwen (1947) recorded fourteen cases with the dysenteric syndrome, one in a woman. Paronen (1948) compiled the largest series of cases of Reiter's disease associated with an epidemic of bacillary dysentery, during the second world war in Finland, and of his 344 patients, 34 (9·9 per cent.) were women. The sex distribution of cases of dysentery in this epidemic is not stated, nor whether there was any difference in the clinical course of Reiter's disease in males and females. Harkness (1950b) could recall seeing only three female patients with polyarthritis, non-gonococcal cervical discharge, and keratoderma. These were presumably examples of the venereally acquired syndrome. Rinkoff (1952) described in detail a woman who developed an attack of Reiter's disease with uveitis; there was no evidence of intestinal infection. Stanworth and Sharp (1956) reported on nine female patients whom they considered had Reiter's disease; three of these had radiographic changes of sacro-iliitis and suffered from attacks of recurrent uveitis. Dysentery was not considered to be an aetiological factor in these cases. More recently Refvem (1957) has reported three further cases.

Material

The present paper deals with case material from two venereal disease clinics in London; the Whitechapel Clinic of the London Hospital, and the Special Clinic, St. Mary's Hospital, Paddington. From the first clinic, ten female cases are reported, but no data on sex incidence are available; 110 cases of Reiter's disease in the male were studied, but these were selected for a variety of reasons. At St. Mary's Hospital, however, information has been collected from all the case records of patients of both sexes attending the clinic over a period of 15 years, and 213 cases of Reiter's disease were found. Of these, four (1·8 per cent.) were females. In all, therefore, fourteen cases in the female were available for study. Two patients had two attacks each (Cases 4 and 12); the others had single attacks.

Clinical Data

Age at Onset.—The range was from 18 to 58 years (mean 32·2).

Race.—All the patients were white, with the exception of Case 11, who was a West African.

Genital Infection.—Seven attacks of arthritis were associated with a gonococcal infection. In three further attacks (Case 4—second attack; Cases 8 and 14) there was presumptive evidence of gonorrhoea, but no bacteriological proof could be obtained. In the remaining six attacks (six patients) the genital infection was of the "non-specific" variety. In two of these cases vaginal discharge preceded the development of arthritis by some weeks;

on examination both patients were found to have large cervical erosions. Two patients began their illness with cystitis, which was haemorrhagic in one case; *B. proteus* was grown from the urine in one patient, but in the other no growth was obtained. In Case 5 no genito-urinary symptoms were noted by the patient until the arthritis had been present in chronic form for 8 years, when she developed cystitis with haematuria and an exacerbation of her arthritis; she was then found to have chronic cervicitis.

Arthritis.—This was present in all cases and in every attack. The joints involved are shown in Table I. In five attacks it was mono-articular, the single joints affected being the knee and shoulder (twice each) and the wrist.

TABLE I
DISTRIBUTION OF JOINTS INVOLVED

Joints Involved	Number of Patients Affected
Knees	11
Wrists	7
Ankles	6
Metatarsophalangeal Joints	5
Shoulder	5
Sacro-iliac Joints	3
Metacarpophalangeal Joints	1

The response to treatment with penicillin was of interest. This drug was administered to all patients in whom gonorrhoea had been diagnosed or the presumptive evidence of infection was strong (ten cases in all). One further patient was given the drug on no very clear grounds. In only one case (Case 3) did the arthritis show any improvement after treatment with penicillin. It is possible, therefore, that this patient may have been suffering from a true gonococcal arthritis.

In two cases, in which the disease pursued a long and chronic course, therapy of all kinds, including steroid hormones and butazolidin, appeared to offer no benefit.

The duration of arthritis varied considerably in sixteen attacks. Details are shown in Table II.

TABLE II
DURATION OF ARTHRITIS IN SIXTEEN ATTACKS

Duration	Number of Attacks
2 mths	5
2–8 mths	6
1–2 yrs	3
6 yrs	1
10 yrs	1

Fasciitis and Tendonitis.—Plantar fasciitis occurred in four cases. Achilles tendonitis and involvement of the extensor tendons of the wrist were seen in one case each.

Eye Involvement.—In seven of the fourteen cases, eye changes were noted. Four patients developed conjunctivitis during their illness, which was complicated in one case by the development of superficial keratitis. Two patients (Cases 7 and 14) developed recurrent iritis over a period of 2 years. One patient had an ulcer of the eye, presumably of the cornea, but this was treated elsewhere and no records are available.

Skin and Mucous Membrane Lesions.—No evidence of these was found in any of the cases.

Radiological Changes.—*X*-ray examination of clinically affected joints and routine films of the heels and sacro-iliac joints were carried out in eight cases. Changes in the sacro-iliac joints with loss of the normal articular outline and subarticular sclerosis were seen in Case 11 (Fig. 1) and also in a less marked degree in Cases 5 and 6.

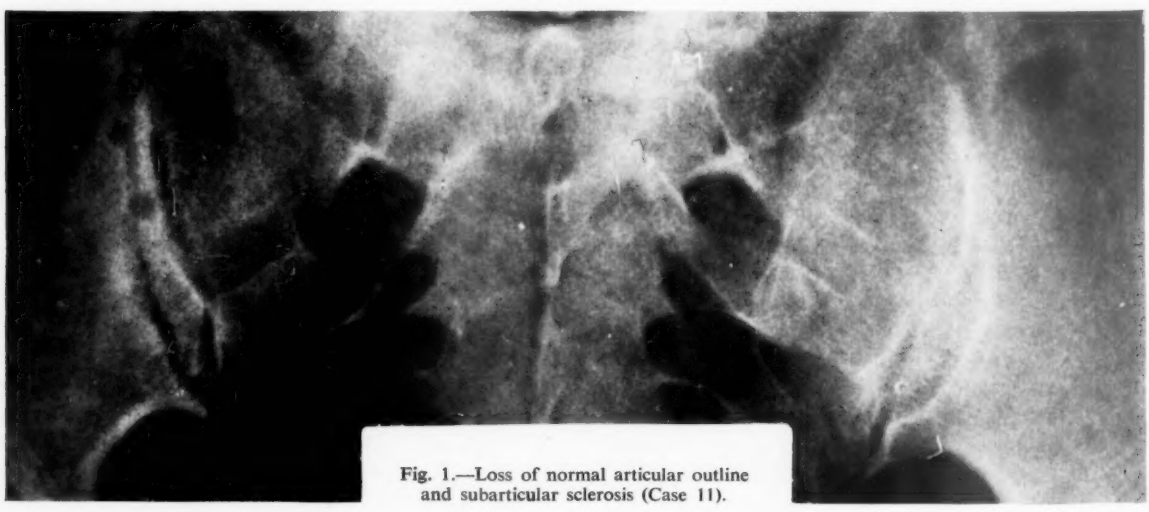

Fig. 1.—Loss of normal articular outline and subarticular sclerosis (Case 11).

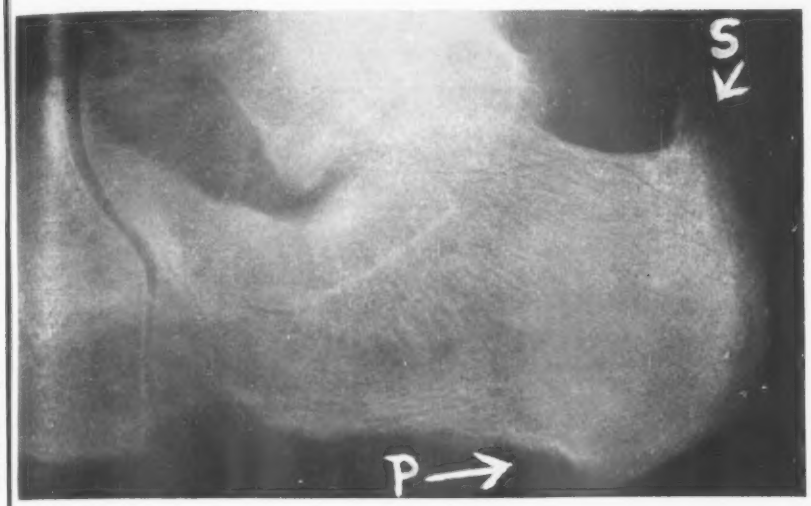

Fig. 2.—Plantar periostitis (P) and posterior spurring (S) of os calcis (Case 5).

Fig. 3.—Periostitis of patella (P) and femur (Case 11).

Posterior and plantar spurring was present in Case 5 (Fig. 2). Small plantar spurs were present in Cases 6, 11, and 12. Periosteal new bone formation, erosions, and cystic changes in the metatarsal bones were found in Cases 6, 12, and 13. Marked periosteal involvement of the patella and adjacent femur was seen in Case 11 (Fig. 3).

Laboratory Findings.—These are summarized in Table III (overleaf). Pleuropneumonia-like organisms (P.P.L.O.) were cultured from the cervices of two patients and a complement-fixation test for P.P.L.O. was positive in a third case. The differential sheep cell agglutination test (Rose-Waaler) was performed in six cases, including three which ran a protracted course, and was negative in all six. The differential blood count was normal in all except two cases in which it was not done. A rectal swab 'grew no dysentery organisms' in three cases and dysentery agglutinations in four 'further cases were all negative'.

Case Reports

Case 1, a single female aged 18, complained of pain and swelling in left knee for 3 days and vague lower abdominal pain of 6 weeks' duration. She denied any genito-urinary symptoms. On examination she had a severe cervicitis, proctitis, and bilateral salpingitis. The left knee was tensely swollen. Gonococci were found in smears from the cervix and rectum. She was admitted to hospital and treatment with intramuscular crystalline penicillin was instituted, a total of 2·4 mega units being given in 7 days. The arthritis of the knee showed no improvement though the salpingitis and cervicitis resolved rapidly. She was then given artificial fever therapy by means of subcutaneous "Pyrifer" vaccine. The arthritis then commenced to improve and there were no abnormal signs to be found in the left knee 6 weeks after admission. *X* ray showed no abnormality.

TABLE III

PATHOLOGICAL FINDINGS IN FOURTEEN WOMEN WITH REITER'S DISEASE

Case No.	Gonococcus		P.P.L.O.		Trichomonas vaginalis	Erythrocyte Sedimentation Rate (Westergren)	Hb (per cent.)	White Blood Cells
	Culture	Complement-Fixation Test	Culture	Complement-Fixation Test				
1	+	−	0	0	+	20	0	7,000
2.	+	−	+	0	−	81	76	9,000
3	+	−	0	0	+	20	75	6,000
4 (1st attack)	+	+	+	0	−	12	0	0
(2nd attack)	−	+	0	0	−	20	0	0
5	−	−	0	0	−	40	77	9,000
6	−	−	0	0	−	91	80	11,000
7	−	−	0	0	−	100	76	8,000
8	−	+	0	0	−	26	0	16,000
9	−	+	0	0	+	40	86	11,000
10	−	−	0	0	−	45	62	8,000
11	+	+	0	−	−	50	100	6,000
12 (1st attack)	−	0	0	0	−	57	95	11,000
(2nd attack)	+	+	0	−	−	50	80	11,000
13	+	+	−	+	+	15	80	8,000
14	−	−	0	0	−	40	85	9,000

+ = Positive; − = Negative; 0 = Not done.

Case 2, a married housewife aged 19, had developed a vaginal discharge 3 months after marriage, and 4 weeks later the left wrist became swollen and painful. Examination showed an acute arthritis of the left wrist and the presence of a severe vaginitis, urethritis, and cervicitis with erosion. The body temperature was 101° F. Cultures from the cervix and urethra were positive for gonococci and pleuropneumonia-like organisms. She was admitted to hospital and treated with 600,000 units procaine penicillin intramuscularly daily for 8 days. There was no immediate response to this treatment, but the joint began to improve after about a week, and cleared completely in a month. She was febrile for 8 days. The erythrocyte sedimentation rate was 81 mm. Hg in one hour (Westergren) and the haemoglobin 76 per cent. *X* ray of the wrist and sacro-iliac joints showed no abnormality.

Since leaving hospital she had had five attacks of gonorrhoea and one attack of "cystitis", but on no occasion did any joint symptoms develop.

Case 3, a married housewife aged 36, complained of pain in both wrists for 4 days. There were no genito-urinary symptoms. She had an acute arthritis of the left wrist and a teno-synovitis of the extensor tendons of the right wrist. Genital examination showed some urethritis and cervicitis, and gonococci were present in smears and cultures from these sites. The patient was admitted to hospital and treatment with procaine penicillin injections 600,000 units daily and sulphatriad 5 g. daily by mouth was begun. The teno-synovitis improved on the fourth day in hospital, but the arthritis of the wrist did not clear up for a further 3 days. During a follow-up period of 8 months the patient remained free of all symptoms.

Case 4, a married housewife aged 37, had noted a vaginal discharge for 7 days, and 3 days before attending had developed lower abdominal pain, pain in the right shoulder, and sore eyes.

She was found to have bilateral conjunctivitis and an acute arthritis of the right shoulder joint. Genital examination revealed the presence of a purulent urethritis and cervicitis, both fallopian tubes being thickened and acutely tender. Smears and cultures were positive for gonococci. After admission to hospital she was treated with 600,000 units procaine penicillin intramuscularly for 10 days. There was no improvement in the arthritis though the abdominal pains and conjunctivitis rapidly subsided. She was eventually subjected to artificial fever therapy by means of subcutaneous "Pyrifer" vaccine, but this also seemed to have little effect. The joint recovered in about 4 weeks' time.

A year later she attended again, this time complaining of lower abdominal pain and pain in the right shoulder for about 16 days. She had attended another hospital for the abdominal pain, where she had received "electrical treatment", and 2 days before attending at the clinic she had developed vaginal discharge and scalding and frequency of micturition. She had an acute arthritis

of the right shoulder joint, a purulent urethral and cervical discharge, and tender swelling of both fallopian tubes. Smears and cultures were negative for the presence of gonococci but the gonococcal complement-fixation test was positive.

She was again admitted to hospital and procaine penicillin 600,000 units daily was given for 10 days by intramuscular injection. Again the arthritis made no response to this treatment though the genito-urinary and abdominal symptoms were quickly relieved. The arthritis subsided gradually, however, and no signs of disease of this joint was present 4 weeks later. She was seen from time to time over a 4-year period, during which she contracted gonorrhoea on four occasions. She had no further arthritic symptoms and no radiographic changes were noted.

Case 5, a married housewife aged 37, gave the following history:

1946: Normal pregnancy and delivery.

1947: Pain in the plantar surface of both heels, not very troublesome except after a lot of walking.

1948: The left ankle became swollen and painful; this lasted a few months and then cleared up only to recur about 14 weeks later. It persisted in this fashion for nearly 2 years.

1951: Pain and swelling of the left knee developed; it waxed and waned in severity, but in general persisted for the next 4 years.

1955: The right knee became swollen and painful. A few months later dysuria, frequency, and haematuria developed, associated with a low grade arthritis of several metatarsophalangeal joints of both feet. The patient felt well throughout the illness.

Both knee joints were slightly painful and there was a small effusion in the left one. There was some thickening of the left ankle joint and tenderness to pressure over the plantar surface of both heel bones. There was a moderate degree of pes planus with early lateral deviation of the toes at the metatarsophalangeal joints. Genital examination revealed a chronic cervicitis. Smears and cultures were negative for gonococci and the complement-fixation test was negative. A biopsy of the cervix showed only "non-specific chronic inflammatory changes". A catheter specimen of urine showed no abnormality (the patient had received treatment for her presumed "cystitis" from her own doctor before admission). The haemoglobin was 80 per cent., the erythrocyte sedimentation rate 40 mm./hr (Westergren) and the blood uric acid 3·2 mg./100 ml. The Rose-Waaler test was negative.

X rays of the wrists and hands showed a small erosion of the right ulna styloid but no other changes. The right sacro-iliac joint was probably abnormal, showing widening and sclerosis of the iliac portion of the base. The ankles showed periosteal new bone formation on both malleoli. Erosions were present in all the metatarsal heads of the left foot. The upper posterior surface of both calcanei showed a partly destructive and proliferative lesion. There was periosteal new bone formation on the plantar surface of both of these bones, particularly the left.

The patient's symptoms, which were not severe, were controlled to some extent by oral phenylbutazone.

Case 6, a married housewife aged 52, enjoyed good health until September, 1956, when she had a severe attack of cystitis treated by her own doctor. In February, 1957, and March, 1957, she had attended an Eye Hospital for the treatment of attacks of conjunctivitis, and 6 months later she developed dysuria, urgency, and terminal haematuria. She was seen in the Surgical Out-Patients Department and a diagnosis of cystitis made. A catheter specimen of urine grew *Bacillus proteus* on culture. She received treatment with sulphonamides by mouth, and the urinary symptoms improved. She then began to complain of pain in the region of the left buttock and in the lumbar region and of feeling generally ill. An irregular fever of up to 101° F. persisted for the next 3 weeks. Arthritis of both knee joints and numerous metatarsophalangeal joints developed; this persisted for about 21 days and then began to improve spontaneously; 8 weeks after the onset of joint symptoms she had a further attack of frequency and dysuria which was associated on this occasion with bilateral conjunctivitis and an exacerbation of the back pain.

Examination showed effusions into both knee joints and tenderness of all metatarsophalangeal joints and of the plantar surface of both heels. Compression of the anterior superior iliac spines produced pain referred to the region of the left sacro-iliac joint. Genital examination showed the presence of a moderate severe cervicitis. Smears and cultures were negative for the presence of gonococci. The erythrocyte sedimentation rate was 90 mm./hr. Fluid aspirated from the right knee was yellow and turbid. The deposit contained many pus cells and occasional lymphocytes; culture was sterile. The Rose-Waaler test was negative on two occasions.

The arthritic pain was not relieved by phenylbutazone, but the arthritis made a slow recovery over a period of about 6 months.

Case 7, a married housewife aged 35, was well until she suffered a prolonged attack of iritis 3 months after the birth of her third child. Eventually both eyes were involved and recurring attacks persisted for about 2 years, when a profuse yellow vaginal discharge with some dysuria developed. A few days later the right knee became swollen and painful. Examination showed an acute iritis of the right eye, and the right knee joint was tense and swollen and all movements limited by pain. There was a severe cervicitis with erosion. Smears and cultures from the cervix and urethra were negative for gonococci. Turbid yellow fluid was aspirated from the knee joint and smears showed many pus cells and some lymphocytes. No organisms were seen and the fluid was sterile after both aerobic and anaerobic cultures. The gonococcal complement-fixation test was negative and the haemoglobin 76 per cent. Treatment with intramuscular streptomycin improved the vaginal symptoms but had no effect on the arthritis. Oral cortisone 50 mg. twice daily for 2 weeks caused lessening of pain and swelling

in the right knee. The dose of cortisone was progressively reduced over the next 2 weeks but the improvement in the knee joint was maintained. The iritis was still active, however, and did not clear up for a further 2 months. 6 months later there was a return of the vaginal discharge associated with a further attack of iritis and a return of pain and swelling in the right knee joint. These symptoms persisted for nearly 6 months, except that the vaginal discharge again showed improvement after streptomycin therapy. Shortly afterwards, the arthritis slowly began to improve. No nodules were found and the lowest haemoglobin value recorded was 76 per cent. The Rose-Waaler test was negative and the erythrocyte sedimentation rate varied from 90 mm./hr at the height of the illness to 6 mm./hr during the stage of remission. The illness lasted for about 3 years and evidence of a low grade arthritis of the right knee was still present at the patient's last attendance.

Case 8, a single female aged 27, had developed a swollen painful right wrist and right ankle 6 months before attendance at the clinic, and had been admitted to another hospital where a diagnosis of infective arthritis was made. The erythrocyte sedimentation rate was 20 mm./hr and the gonococcal complement-fixation test was positive. She had received treatment with intramuscular penicillin 4-hrly for 7 days but details of the dosage were not available. There was no response to this therapy but some improvement occurred later after rest in bed. She was eventually referred to the clinic on account of the serological findings, and was then complaining only of slight pain in the right wrist.

On examination there was slight tenderness and swelling of the right wrist joint. Genital examination showed the presence of a moderately severe cervicitis with erosion. Smears and cultures were repeatedly negative for the presence of gonococci, but the gonococcal complement-fixation test was strongly positive. The erythrocyte sedimentation rate was 27 mm./hr. A trial of fever therapy by means of intramuscular Pyrolactin produced no effect on the arthritis which gradually improved, subsiding completely in about 12 months' time.

Case 9, a single female aged 19, developed an "ulcer at the angle of the eye" after sexual intercourse with a casual acquaintance. She had been treated with eye drops at another hospital but no details were available. A week later she had developed a vaginal discharge with some frequency, and 3 days later her right knee and ankle became swollen and painful, and this was followed by similar symptoms in the right wrist.

Examination revealed an acute arthritis of the right ankle, wrist, and knee joint. The body temperature was 101° F. and the pulse rate 100. A cervical culture was negative for the presence of gonococci. She received treatment with crystalline penicillin, 250,000 units intramuscularly twice daily, and oral sulphonamides (5 g. daily). Genital examination after 2 days of this treatment showed a moderate degree of vaginitis and cervicitis. No gonococci were found in smears and none were grown in culture. Many trichomonas were present in the vaginal smear. The arthritis made no response to chemotherapy but began to improve about 2 weeks after admission. The erythrocyte sedimentation rate was 40 mm./hr and the haemoglobin 83 per cent. The gonococcal complement-fixation test was negative.

After discharge from hospital the patient had three attacks of gonorrhoea but experienced no further joint symptoms.

Case 10, a married housewife aged 23, had developed dysuria, frequency, and vaginal discharge 5 days before admission, 3 days later the right shoulder became painful to move, and the next day the left wrist became swollen and painful.

She looked ill and was in severe pain, with body temperature 100·4° F., and pulse rate 88. There was an acute arthritis of the left wrist and right shoulder with restriction of all movements by pain. Genital examination revealed a purulent urethritis, vaginitis, and cervicitis with erosion. Smears and culture were positive for gonococci from the urethra and cervix. She received an injection of 1 mega unit crystalline penicillin intramuscularly and was then admitted to hospital, where procaine penicillin 600,000 units intramuscularly was given daily for 5 days. The fever continued and there was no improvement in her arthritis. Following treatment with 25 mg. ACTH intramuscularly every 6 hours, the joint condition improved rapidly and the pain subsided. The injections were stopped after 6 days and there was an immediate return of pain and swelling in the shoulder and wrist and the temperature rose to 100° F. Penicillin 600,000 units intramuscularly daily was resumed without apparent effect. She remained in hospital for 6 weeks and on discharge the joints were normal, the erythrocyte sedimentation rate was 60 mm./hr falling to 20 mm./hr, and an *x* ray of the affected joints showed no abnormality.

Case 11, a single West African female aged 26, was admitted to hospital with gonococcal salpingitis; 3 weeks after penicillin treatment she developed arthritis of both knees, and the right ankle, right hip, and left shoulder. Penicillin in large doses had no effect on the course of the arthritis which persisted with little change for 3 years. At that time she began to complain of pain and morning stiffness in the neck and lower back. During the following year the joints improved when she had an attack of bilateral conjunctivitis; 3 months later and one year later the conjunctivitis recurred. When she was last seen, 7½ years after the onset of her illness, she was quite well, except for occasional discomfort in the lumbar region. *X*-ray examination showed marked changes in the knee joints and right sacro-iliac joint (Fig. 3).

Case 12, a married female aged 49, had attended another hospital with a vaginal discharge which was followed within 2 weeks by arthritis involving the ankles, right wrist, several metatarsophalangeal joints, and the cervical spine. Genital investigation failed to show the gonococcus. This attack lasted 4 months, and 3 years later the patient again noticed a vaginal discharge,

followed 2 weeks later by bilateral conjunctivitis, and 2 days later by polyarthritis and plantar fasciitis. The body temperature rose to 103° F. during the first 3 days of the arthritis, and the white blood count was 11,000 per c.mm. with 81 per cent. neutrophils. Genital examination showed cervicitis from which gonococci were grown. Penicillin had no effect on the arthritis, which lasted for about 2 months, but was successful in clearing the gonorrhoea. During this time the eyes again became inflamed and dendritic corneal ulcers developed. When seen 3 months later, she had completely recovered, but *x* rays showed periosteal new bone formation around the neck of the third left metatarsal and small bilateral calcaneal spurs.

Case 13, a married female aged 25, gonorrhoea from her husband and remained untreated for 3 months, 2 weeks after she first noticed the vaginal discharge, she developed pains in both shoulders and the lower back, which lasted for 6 months and was not influenced by penicillin therapy. She had three attacks of gonorrhoea without any complications 3 years later, and a year later cystitis developed. The urine was sterile on bacteriological investigation. A month later extensive polyarthritis, Achilles tendonitis, and sacro-iliitis developed. On genital examination urethritis and cervicitis was found but neither gonococci nor P.P.L.O. were grown. The arthritis did not respond to penicillin or prednisone 20 mg. daily for 4 weeks, but phenylbutazone 400 mg. daily appeared to relieve the symptoms. At present the disease is still active in the joints, some 5 years after the onset. There was no anaemia during the course of the illness. *X* rays showed some erosions of the metatarsal bones on both sides; the other joints, including the sacro-iliacs, appeared to be normal.

Case 14, a married woman aged 58, gave a history of vaginitis, followed within a month by arthritis involving the right knee and several toes, and plantar fasciitis on the right side. A month later iritis developed and this had recurred several times over the next 2 years. Gonococci were not isolated from the genital tract and the arthritis did not respond to intramuscular penicillin injections. At present, 2 years after the onset of the arthritis the patient is convalescing.

Discussion

The course of the arthritis in two patients (Cases 5 and 11) was of much longer duration than the others, and persisted for approximately 10 and 6 years respectively. Such chronicity suggests the possibility of rheumatoid arthritis as an alternative diagnosis. This is considered unlikely, however, as in Case 11 the onset was closely associated with genital infection, attacks of conjunctivitis occurred during the illness, and radiographic changes typical of Reiter's disease developed in the right sacro-iliac joint, patella, and adjacent tibia (Figs 1 and 3). No rheumatic nodules were present and the Rose-Waaler test (D.A.T.) was negative. In Case 5 the association with genital disease was less clear. However, the deformity of the feet was characteristic of Reiter's disease as was the development of the plantar periosteal reaction (Fig. 2) and other typical radiographic changes (Mason, Murray, Oates, and Young, 1959). No rheumatic nodules were found and the Rose-Waaler test was negative. Neither patient showed the malaise, weight loss, and other evidence of systemic reaction which is seen so commonly in young women with rheumatoid arthritis.

In seven patients gonococci were cultured from the genital tract, and in three of them (Cases 1, 2, and 4) the arthritis was mono-articular. Though no joint and fluid studies were carried out in these patients the complete lack of response to adequate courses of intramuscular penicillin was strong evidence against the possibility that the arthritis was gonococcal.

The truth of the statement that Reiter's disease is uncommon in the female appears to be confirmed by our experience. In none of the fourteen patients was there any evidence of intestinal infection and the association of the attacks with gonorrhoea on seven and possibly ten occasions, makes it likely that all were examples of the venereally acquired syndrome. Some of these patients had multiple genital infections and not every attack was followed by arthritis. Why the disease should attack the male in the majority of instances is an unsolved problem. Men in general tend to be more promiscuous sexually than women and would therefore be more likely to acquire the venereal form of the disease in greater numbers. There is, however, no evidence at present that Reiter's disease occurs more commonly amongst prostitutes than among women generally. In addition, although the female contacts of patients with Reiter's disease are frequently found to be suffering from non-specific genital infection, they rarely, if ever, are found to be suffering from arthritis or uveitis. Possibly the degree of disproportion is more apparent than real; for example, in this series, the genito-urinary symptoms included vaginal discharge, dysuria, and frequency of micturition, but complaints of this nature are common, especially in parous women, and do not always lead to medical investigation. The possibility that female patients with Reiter's disease may be diagnosed as suffering from other rheumatic diseases should not be discounted.

With such a small series of patients, it is not profitable to make many comparisons about the course of the disease in the two sexes. However, the general pattern seen in the male patients was

also observed in the females, including some in which the disease pursued a prolonged chronic course. Possibly, mono-articular forms were commoner than might have been expected from the experience in male patients. Csonka (1958), for instance, found that 7 per cent. of his 209 male patients had one joint involved, against 31 per cent. in the present series. Clinical evidence of sacro-iliitis was found in two cases and radiographic changes, identical with those described in men (Murray, Oates, and Young, 1958; Reynolds and Csonka, 1958) were found in three others.

Summary

(1) The literature relating to Reiter's disease in the female is briefly reviewed.

(2) Fourteen cases of Reiter's disease in the female are described, and the clinical course and accessory findings are shown to be similar to those seen in males.

(3) The incidence of Reiter's disease in females compared with that in males is low, though the possibility of misdiagnosing such cases is probably higher than in the male.

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La maladie de Reiter chez la femme

RÉSUMÉ

(1) On passe en revue la littérature concernant la maladie de Reiter chez la femme.

(2) On décrit 14 cas de maladie de Reiter chez la femme et on montre que l'évolution clinique et les données accessoires sont les mêmes que chez l'homme.

(3) La fréquence de la maladie de Reiter chez la femme, en comparaison à l'homme, est basse, bien que la possibilité d'une erreur diagnostique en tels cas est probablement plus grande que chez les hommes.

La enfermedad de Reiter en la mujer

SUMARIO

(1) Se pasa en revista la literatura respecto a la enfermedad de Reiter en la mujer.

(2) Se describen 14 casos de enfermedad de Reiter en mujeres y se demuestra que la evolución clínica y los datos accesorios se parecen a los del hombre.

(3) La incidencia de la enfermedad de Reiter en la mujer, comparada con la en el hombre, es baja, aunque la posibilidad de un error diagnóstico en tales casos es probablemente mayor que en el hombre.

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"RHEUMATIC" IRITIS AND IRIDOCYCLITIS

BY

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Every text-book of ophthalmology mentions "rheumatic" iritis and iridocyclitis, either as the sole manifestation of the rheumatic state or as one of a series of rheumatic symptoms. It appears, however, that this type of eye lesion is not associated with rheumatic conditions in general, but only with the clearly defined complaint known as ankylosing spondylitis.

We have studied some thousands of patients with rheumatic fever and have very rarely seen any ocular complications or iritis or iridocyclitis in particular. In no case has iritis been observed in an acute attack of rheumatic fever. It may be that our mode of treating rheumatic fever is so intensive and effective that eye complications do not develop, but we also have numerous patients who have undergone less thorough treatment elsewhere, and these cases also have been quite free from lesions of the iris. If rheumatic fever and iritis do appear together, therefore, their coincidence must be regarded as occurring by chance.

We have also had under our care tens of thousands of patients suffering from rheumatoid arthritis, and many of them have been under observation for many years, but lesions of the iris have been so rare that they cannot be regarded as complications of the arthritic condition.

The same may be said about degenerative joint disease, whether it affects the joints of the extremities (osteo-arthrosis) or of the vertebral column (spondylosis or spondylarthrosis deformans). The appearance of an iris lesion is so unusual that it is obviously unrelated to the articular disease.

However, the problem presents itself in quite a different light when considered in connexion with ankylosing spondylitis. Some dozens of cases have sufficed to prove that these ocular complications accompany the spinal lesions too often to be due to chance. Even if iritis and iridocyclitis cannot be accepted as complications in the other rheumatic conditions listed above, there seems to be no doubt that they quite frequently belong to the clinical picture of ankylosing spondylitis.

Previous Investigations

Graber-Duvernay (1944) found iritis or iridocyclitis in eleven of 33 patients with ankylosing spondylitis (33 per cent.). Schley (1937), who examined the lumbar spine of 73 patients suffering from "rheumatic iritis", was able to detect ankylosing spondylitis in 12·5 per cent. of them. We have the impression that this author did not devote enough attention to a careful study of the sacroiliac joint, the changes of which are usually specific, especially in the diagnosis of early cases. Had this joint been examined more closely, the number of positive cases would probably have been greater.

Ravault and Berthier (1944) discovered eight cases of iritis or iridocyclitis in 28 cases of ankylosing spondylitis (35 per cent.).

Michaud and Forestier (1954) saw *uveal* lesions only in seventeen of 200 patients with ankylosing spondylitis (8·5 per cent.), but they point out that this must be considered as a very low figure because many of their cases were relatively recent ones.

Françon (1946) estimated the frequency of uveal manifestations at 60 per cent., but without giving precise statistical data.

Iritis and iridocyclitis were seen in 25 of 184 cases (13·5 per cent.) reported by Hart and Maclagan (1955).

Present Series of Cases

In our clinic we have seen over a thousand cases of ankylosing spondylitis in the last 20 or 30 years, and we have followed the majority of them for long periods.*

It was decided to ascertain what proportion of them had suffered from iritis and iridocyclitis, since

* These patients have founded a sports club called by them the O'Connor-Pierre Marie-Bechterew Sports Club, which unites them not only in sport, but also in social activities as a sort of a family of rheumatics all afflicted with the same handicap. We have made an instructive film showing the sporting activities of this unusual club. The "Triumphal March" of the International League against Rheumatism, skilfully composed by Serge Larsen, the son of the much regretted French rheumatologist, Mathieu-Pierre Weil, was sung by the choir of this club and broadcast by the Bratislava broadcasting corporation in 1953. It was without doubt the first occasion on which this March was broadcast.

statistics had not previously been compiled for such a large series.

For various reasons it was impossible for us to re-examine all our patients and we were obliged to satisfy ourselves with checking 625 cases (570 males and 55 females).

Undoubted uveal affections were seen in 179 (28·9 per cent.), which included 163 men and sixteen women. These cases are distributed by age and sex in Table I.

As our standard was rather too strict than too liberal, this percentage does not by any means represent a maximum. In spite of the thoroughness with which we tried to discover all cases of iritis and iridocyclitis, we omitted those in which the diagnosis was at all doubtful.

In the second part of our study we examined a series of cases of iritis and iridocyclitis, the aetiology of which was obscure to the ophthalmologists, to find out whether unrecognized incipient ankylosing spondylosis was associated with the eye lesions. We assumed that such cases had developed subclinically or that the symptoms of spinal involvement had been so slight that the patient had paid no attention to them. If severe pain had occurred intermittently it was possible that neither the patient nor his doctor had suspected that the ocular lesions had any connexion with sporadic attacks of "lumbago" or "sciatica".

By arrangement with the First Clinic of Ophthalmology, all cases of iritis and iridocyclitis which fitted this description were referred to us, and we examined 474 patients with uveal lesions (269 males and 205 females), who are distributed by age groups in Table II (opposite).

Among these 474 patients with iritis and iridocyclitis we found 91 with ankylosing spondylitis (17·4 per cent.), comprising 83 males (30·8 per cent.) and eight females (3·9 per cent.). In men the disease was found in all age groups from 20 to 90 years, but in women only in the middle age groups from 30 to 60 years. With only one exception the age distribution was exactly the same as in the series of ankylosing spondylitis patients with iritis.

Treatment.—One of our cases of ankylosing spondylitis seems to deserve special mention. A teacher at a technical college, aged 51, had suffered for many years with repeated attacks of iritis and iridocyclitis, each lasting at least one month and some as long as 3 months. As he had regularly two attacks annually he was very often unable to work for 6 months of the year. In 1950, however, we prescribed cortisone ointment for local ophthalmic use just at the onset of a new attack of iritis. The effect was spectacular; all ocular signs disappeared within 48 hours, although the patient could not remember any previous occasion when the inflammation of the iris had subsided in less than 30 days. He was advised to apply the ointment, in the future, immediately he felt the first symptoms of ocular involvement, and has since succeeded in keeping every threatened attack at bay, and has not lost a day's work in 6 years.

Summary

(1) Iritis and iridocyclitis do not appear more frequently in patients suffering from rheumatic fever or rheumatoid arthritis than in patients with other diseases or in persons in good health.

(2) Patients with degenerative joint disease of the extremities or of the spine manifest iritis and iridocyclitis only with extreme rarity.

(3) Iritis and iridocyclitis frequently accompany ankylosing spondylitis. Different authors have

TABLE I

CASES OF ANKYLOSING SPONDYLITIS IN WHICH IRITIS WAS ALSO PRESENT, BY AGE AND SEX

Age Group (yrs)	Males			Females			Total		
	Iritis	Without Iritis	Total	Iritis	Without Iritis	Total	Iritis	Without Iritis	Total
11–20	0	5	5	1	1	2	1	6	7
21–30	8	35	43	0	5	5	8	40	48
31–40	25	90	115	3	12	15	28	102	130
41–50	55	132	187	6	15	21	61	147	208
51–60	49	111	160	4	3	7	53	114	167
61–70	23	31	54	2	2	4	25	33	58
71–80	2	2	4	0	1	1	2	3	5
81–90	1	1	2	0	0	0	1	1	2
Total No.	163	407	570	16	39	55	179	446	625
Per cent.	28·6	71·4	100	29·1	70·9	100	28·9	71·1	100

TABLE II

CASES OF IRITIS AND IRIDOCYCLITIS IN WHICH ANKYLOSING SPONDYLITIS WAS DETECTED, BY AGE AND SEX

Age Group (yrs)	Males			Females			Total		
	Spine Negative	Ankylosing Spondylitis	Total	Spine Negative	Ankylosing Spondylitis	Total	Spine Negative	Ankylosing Spondylitis	Total
11–20	2	0	2	4	0	4	6		6
21–30	12	6	18	23	0	23	35	6	41
31–40	28	10	38	17	1	18	45	11	56
41–50	52	25	77	48	5	53	100	30	130
51–60	56	23	79	57	2	59	113	25	138
61–70	23	16	39	35	0	35	58	16	74
71–80	12	2	14	12	0	12	24	2	26
81–90	1	1	2	1	0	1	2	1	3
Total No.	186	83	269	197	8	205	383	91	474
Per cent.	69·1	30·9	100	96·1	3·9	100	80·8	19·2	100

estimated the frequency of these ocular complications at from 10 to 60 per cent., but their findings have not been checked against a sufficiently large series of cases.

(4) The authors have carefully re-examined 625 subjects with ankylosing spondylitis and have ascertained that 179 (28·9 per cent.) had undoubtedly suffered from uveal lesions. This included 163 of 570 males (28·6 per cent.) and 16 of 55 females (29·1 per cent.).

(5) The authors have also examined 474 adult patients with iritis or iridocyclitis of unknown aetiology. Among 269 males 83 cases of unsuspected ankylosing spondylitis were found (30·8 per cent.) and among 205 females only eight such cases (3·9 per cent.).

(6) The conclusion is drawn that every case of iritis and iridocyclitis of unknown origin should be examined for latent or incipient ankylosing spondylitis.

(7) When such attacks of iritis occur they can be treated with local cortisone ointment.

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Irite et iridocyclite "rhumatismales"

RÉSUMÉ

(1) L'irite et l'iridocyclite ne surviennent pas plus souvent au cours du rhumatisme articulaire aigu ou de l'arthrite rhumatismale que chez des sujets sains ou atteints d'autres maladies.

(2) Les sujets atteints de maladies dégénératives articulaires des extrémités ou du rachis ne souffrent que très rarement d'irite ou d'iridocyclite.

(3) L'irite et l'iridocyclite accompagnent souvent la spondylarthrite ankylosante. De différents auteurs ont estimé la fréquence de ces complications oculaires à de 10 à 60 pour cent, mais leurs résultats n'ont pas été vérifiés par un nombre suffisant des cas.

(4) Les auteurs ont re-examiné soigneusement 625 sujets atteints de spondylarthrite ankylosante et trouvé que 179 (28,9%) d'entre eux avait certainement eu des lésions uvéales. Ce nombre comprenait 163 sur 570 hommes (28,6%) et 16 sur 55 femmes (29,1%).

(5) Les auteurs ont aussi examiné 474 malades adultes atteints d'irite ou d'iridocyclite d'étiologie inconnue. Parmi 269 mâles on a trouvé 83 cas de spondylarthrite ankylosante insoupçonné, mais parmi 205 femelles on n'en a trouvé que huit.

(6) On en tire la conclusion que dans chaque cas d'irite ou d'iridocyclite d'origine inconnue on doit rechercher la spondylarthrite ankylosante, latente ou naissante.

(7) Chaque attaque d'une telle irite peut être traitée par une pommade oculaire à la cortisone.

Iritis e iridociclitis "reumáticas"

SUMARIO

(1) La iritis y la iridociclitis no ocurren más a menudo en el curso del reumatismo poliarticular agudo o de la artritis reumatoide que en otras enfermedades o en sujetos sanos.

(2) Los sujetos con enfermedades degenerativas articulares de las extremidades o de la columna vertebral padecen muy raramente de iritis o de iridociclitis.

(3) La iritis y la iridociclitis acompañan frecuentemente la espondilartritis anquilosante. Varios autores han estimado la frecuencia de estas complicaciones oculares a de 10 a 60 por ciento, pero estos datos no fueron averiguados por un número suficiente de casos.

(4) Los autores re-examinaron cuidadosamente 625 casos con espondilartritis anquilosante y encontraron que 179 (28,9%) de estos habían indudablemente tenido lesiones uveales. Este nombre comprende 163 de 570 hombres (28,6%) y 16 de 55 mujeres (29,1%).

(5) Los autores investigaron también 474 enfermos adultos con iritis o iridociclitis de origen desconocida. Entre 269 hombres encontraron 83 casos de espondilartritis anquilosante no sospechados, pero sólo ocho entre 205 mujeres.

(6) Se concluye que en cada caso de iritis o de iridociclitis de origen desconocido, se debe buscar la espondilartritis anquilosante, latente o naciente.

(7) Ataques de iritis de este tipo pueden tratarse con aplicaciones locales de cortisona.

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DIAGNOSTIC CRITERIA FOR RHEUMATOID ARTHRITIS
1958 REVISION

BY

A COMMITTEE OF THE AMERICAN RHEUMATISM ASSOCIATION

(*Chairman:* DR. M. W. ROPES)

The criteria proposed for diagnostic classification of patients with rheumatoid arthritis have been in use for two years (Ropes, Bennett, Cobb, Jacox, and Jessar, 1956, 1957). During this period many comments have been received, the majority of which have been favourable. There have been, however, criticisms and suggestions which have formed the basis of this revision of the original criteria.

It has become apparent that the criteria are not quite rigorous enough. There has been rather general agreement that in addition to the three present groups there should be a group with even more strict criteria. In such a group the diagnosis of rheumatoid arthritis will be as certain as is possible with our present knowledge about and concept of the disease. The requirements for classification in this group are seven of the eleven criteria listed under the present heading of "Definite Rheumatoid Arthritis", and the new group is to be called "Classical Rheumatoid Arthritis". The significance of the other groups will remain unchanged. In the definite group there should be almost no question that every patient has rheumatoid arthritis, but in the new group more evidence for the diagnosis will usually be available in the form of *x*-ray changes, nodules, "rheumatoid factor", changes in synovial mucin, or characteristic histological findings.

Another point which has caused some discussion is the question of the duration of joint symptoms. The earlier criteria did not state whether the total duration of 6 weeks must be continuous, and whether each one of the symptoms must have been of 6 weeks' duration. The revised criteria require that the joint signs or symptoms in Criteria 1 to 5 must be continuous for at least 6 weeks in the Classical and Definite groups. In the case of the "Probable Rheumatoid Arthritis" group, the required duration is changed from 4 weeks to 6 weeks to lessen the confusion that has arisen in using different durations for the Definite and Probable groups. In only one of the Criteria 1 to 5, however, need the signs or symptoms last the entire 6 weeks to qualify for the Probable group.

A question has arisen whether the criteria necessary for classification into any group must all be present simultaneously. It is our impression that usually the manifestations would all be present at the same time, but we do not consider such a situation necessary for placing a patient into any group.

Some difficulty was encountered in deciding which tests for the so-called "rheumatoid factor" should be accepted for Criterion 8. Many methods are being used and the relative diagnostic value of the various tests is not yet known. We suggest that any method may be used for demonstration of the rheumatoid factor that has been proved by at least two laboratories to be positive in not over 5 per cent. of normal controls.

The other questions that have arisen have been concerned with the "Exclusions". One more exclusion should be added: No. 20 "Agammaglobulinaemia". In this way the poorly understood rheumatic disease that occurs in patients with little or no gamma globulin will be excluded. The "L.E. cell" exclusion, No. 2, offers a more complicated problem, as the reported incidence increases of lupus erythematosus cells in patients with typical clinical pictures of rheumatoid arthritis and no characteristics (such as rash or renal involvement) strongly suggestive of disseminated lupus erythematosus. In the revised criteria, patients with a high concentration of lupus erythematosus cells (as in Exclusion 2) are still to be excluded from the rheumatoid categories, but are to be listed separately and discussed simultaneously with rheumatoid patients if they satisfy the present criteria and exclusions in every respect except Exclusion 2. In regard to the exclusion of gout, it should be pointed out that an increased level of uric acid in the blood does not necessarily exclude a diagnosis of rheumatoid arthritis.

REVISED CRITERIA

Classical Rheumatoid Arthritis

This diagnosis requires seven of the following criteria. In Criteria 1 to 5 the joint signs or symptoms must be continuous for at least 6 weeks. (Any one of the features listed under "EXCLUSIONS" will exclude a patient from this category.)

(1) Morning stiffness.

(2) Pain on motion or tenderness in at least one joint (observed by a physician).

(3) Swelling (soft tissue thickening or fluid—not bony overgrowth alone) in at least one joint (observed by a physician).

(4) Swelling (observed by a physician) of at least one other joint (any interval free of joint symptoms between the two joint involvements may not be more than 3 months).

(5) Symmetrical joint swelling (observed by a physician) with simultaneous involvement of the same joint on both sides of the body (bilateral involvement of mid-phalangeal, metacarpophalangeal, or metatarsophalangeal joints is acceptable without absolute symmetry). Terminal phalangeal joint involvement will not satisfy this criterion.

(6) Subcutaneous nodules (observed by a physician) over bony prominences, on extensor surfaces, or in juxta-articular regions.

(7) *X*-ray changes typical of rheumatoid arthritis (which must include at least bony decalcification localized to or greatest around the involved joints and not just degenerative changes)—degenerative changes do not exclude patients from any group classified as rheumatoid arthritis.

(8) Positive agglutination test—demonstration of the "rheumatoid factor" by any method that, in two laboratories, has been positive in not more than 5 per cent. of normal controls; or positive streptococcal agglutination test.

(9) Poor mucin precipitate from synovial fluid (with shreds and cloudy solution).

(10) Characteristic histological changes in synovial membrane with three or more of the following: marked villous hypertrophy; proliferation of superficial synovial cells often with palisading; marked infiltration of chronic inflammatory cells (lymphocytes or plasma cells predominating) with tendency to form "lymphoid nodules"; deposition of compact fibrin, either on surface or interstitially; foci of cell necrosis.

(11) Characteristic histological changes in nodules showing granulomatous foci with central zones of cell necrosis, surrounded by proliferated fixed cells, and peripheral fibrosis and chronic inflammatory cell infiltration, predominantly perivascular.

Definite Rheumatoid Arthritis

This diagnosis requires five of the above criteria. In Criteria 1 to 5 the joint signs or symptoms must be continuous for at least 6 weeks. (Any one of the features listed under "EXCLUSIONS" will exclude a patient from this category.)

Probable Rheumatoid Arthritis

This diagnosis requires three of the above criteria. In at least one of the Criteria 1 to 5 the joint signs or symptoms must be continuous for at least 6 weeks. (Any one of the features listed under "EXCLUSIONS" will exclude a patient from this category.)

Possible Rheumatoid Arthritis

This diagnosis requires two of the following criteria, and the total duration of joint symptoms must be at least 3 weeks. (Any one of the features listed under "EXCLUSIONS" will exclude a patient from this category.)

(1) Morning stiffness.

(2) Tenderness or pain on motion (observed by a physician) with history of recurrence or persistence for 3 weeks.

(3) History or observation of joint swelling.

(4) Subcutaneous nodules (observed by a physician).

(5) Raised erythrocyte sedimentation rate or C-reactive protein.

(6) Iritis.

Exclusions

(1) The typical rash of *disseminated lupus erythematosus*, with butterfly distribution, follicle plugging, and areas of atrophy.

(2) High concentration of *lupus erythematosus* cells (four or more in two smears prepared from heparinized blood incubated for not more than 2 hrs).

(3) Histological evidence of *periarteritis nodosa*, with segmental necrosis of arteries associated with nodular leucocytic infiltration extending perivascularly and tending to include many eosinophils.

(4) Weakness of neck, trunk, and pharyngeal muscles, or persistent muscle swelling of *dermatomyositis*.

(5) Definite *scleroderma* (not limited to the fingers).

(6) A clinical picture characteristic of *rheumatic fever*, with migratory joint involvement and evidence of endocarditis, especially if accompanied by subcutaneous nodules or erythema marginatum or chorea. (A raised antistreptolysin titre will not rule out the diagnosis of rheumatoid arthritis.)

(7) A clinical picture characteristic of *gouty arthritis*, with acute attacks of swelling, redness, and pain in one or more joints, especially if relieved by colchicine.

(8) Tophi.

(9) A clinical picture characteristic of *acute infectious arthritis* of bacterial or viral origin with

an acute focus of infection or in close association with a disease of known infectious origin; chills; fever; an acute joint involvement, usually migratory initially (especially if there are organisms in the joint fluid or response to antibiotic therapy).

(10) *Tubercle bacilli* in joints or histological evidence of joint tuberculosis.

(11) A clinical picture characteristic of *Reiter's syndrome*, with urethritis and conjunctivitis associated with acute joint involvement, usually migratory initially.

(12) A clinical picture characteristic of the *shoulder-hand syndrome*, with unilateral involvement of shoulder and hand, with diffuse swelling of the hand followed by atrophy and contractures.

(13) A clinical picture characteristic of *hypertrophic pulmonary osteo-arthropathy*, with clubbing of fingers and/or hypertrophic periostitis along the shafts of the long bones especially if an intrapulmonary lesion is present.

(14) A clinical picture characteristic of *neuro-arthropathy*, with condensation and destruction of bones of involved joints and with associated neurological findings.

(15) *Homogentisic acid* in the urine detectable grossly with alkalinization.

(16) Histological evidence of *sarcoid* or a positive Kveim test.

(17) *Multiple myeloma* as evidenced by marked increase in plasma cells in the bone marrow or by Bence-Jones protein in the urine.

(18) Characteristic skin lesions of *erythema nodosum*.

(19) *Leukaemia* or *lymphoma*, with characteristic cells in peripheral blood, bone marrow, or tissues.

(20) *Agammaglobulinaemia*.

It is hoped that these revised criteria will aid in obtaining even more uniformity in the classification of patients with rheumatoid arthritis. Comments and suggestions for modifications or clarification will be welcomed. The criteria should be reviewed in two or three years and revised as necessary.

REFERENCES

Ropes, M. W., Bennett, G. A., Cobb, S., Jacox, R., and Jessar, R. A. (1956). *Bull. rheum. Dis.*, 7, 121.
——, ——, ——, ——, —— (1957). *Ann. rheum. Dis.*, **16**, 118.

Critères diagnostiques pour l'arthrite rhumatismale. Revision, 1958

Arthrite Rhumatismale Classique

Ce diagnostic nécessite sept des critères énumérés ci-dessous. Pour satisfaire les critères 1 à 5 les signes et les symptômes articulaires doivent être continus depuis au moins six semaines. (L'un quelconque des caractères énumérés sous le titre "Exclusions" exclura le malade de cette catégorie).

1. Enraidissement matinal.
2. Mouvement douloureux ou sensibilité dans une articulation au moins (observés par un médecin).
3. Tuméfaction (observée par un médecin) d'une articulation au moins (épaississement du tissu mou ou excès de liquide et non pas excroissance osseuse seule).
4. Tuméfaction (observée par un médecin) d'au moins une autre articulation (toute période de temps sans symptômes articulaires, s'écoulant entre les implications des deux articulations, ne doit pas dépasser trois mois).
5. Tuméfaction articulaire symétrique (observée par un médecin) avec atteinte simultanée de la même articulation de deux cotés du corps (l'atteinte bilatérale des articulations mi-phalangiennes, métacarpo-phalangiennes ou métatarso-phalangiennes est acceptable sand symétrie absolue). L'atteinte de l'articulation phalangienne terminale ne satisfait pas ce critère.
6. Nodules sous-cutanés (observés par un médecin) sur des proéminences osseuses, dans la région des extenseurs ou juxta-articulaires.
7. Altérations radiologiques typiques d'arthrite rhumatismale (devant comprendre au moins une décalcification osseuse localisée ou prédominante aux articulations atteintes et non pas des signes de dégénérescence seuls)—les signes de dégénérescence n'excluent pas les malades du groupe d'arthrite rhumatismale.
8. Réaction d'agglutination positive—mise en evidence du "facteur rhumatismal" par une méthode quelconque qui, dans deux laboratoires, n'a donné plus de 5 pour cent de résultats positifs chez des témoins normaux; ou réaction d'agglutination streptococcique positive.
9. Faible précipité de mucine du liquide synovial (avec fibres et solution trouble).
10. Altérations histologiques caractéristiques de la membrane synoviale, dont trois ou plus des suivantes: hypertrophie villeuse marquée; prolifération des cellules synoviales superficielles, souvent avec palissage; infiltration marquée par éléments inflammatoires chroniques (lymphocytes ou éléments plasmatiques prédominant) avec tendance à former des "nodules lymphoïdes"; depôt de fibrine compacte soit en surface, soit interstitiellement; foyers de nécrose cellulaire.
11. Altérations histologiques caractéristiques des nodules, comprenant des foyers granulomateux avec zones centrales de nécrose cellulaire, entourées de cellules proliférantes fixes, de fibrose périphérique et d'infiltration cellulaire inflammatoire chronique essentiellement périvasculaire.

Arthrite Rhumatismale Definie

Ce diagnostic nécessite cinq des critères énumérés ci-dessus. Dans les critères 1 à 5 les signes et les symptômes articulaires doivent êtres continus pendant au moins six semaines. (L'un quelconque des caractères énumérés sous le titre "Exclusions" exclura le malade de cette catégprie.)

Arthrite Rhumatismale Probable

Ce diagnostic nécessite trois des critères énumérés ci-dessus. Dans un au moins des critères 1 à 5 les signes et les symptômes articulaires doivent être continus pendant au moins six semaines. (L'un quelconque des

caractères énumérés souls le titre "EXCLUSIONS" exclura le malade de cette catégorie.)

ARTHRITE RHUMATISMALE POSSIBLE

Ce diagnostic nécessite deux des critères suivants, et la durée totale des symptômes articulaires doit être au moins de trois semaines. (L'un quelconque des caractères énumérés sous le titre "EXCLUSIONS" exclura le malade de cette catégorie):

1. Enraidissement matinal.
2. Sensibilité ou mouvement douloureux (observés par un médecin) avec antécédants de récurrence ou de persistance pendant trois semaines.
3. Antécédents ou constatation de tuméfaction articulaire.
4. Nodules sous-cutanés (observés par un médecin).
5. Vitesse de sédimentation érythrocytaire élevée ou présence de protéine C-réactive.
6. Irite.

EXCLUSIONS

1. L'éruption typique de *lupus érythémateux disséminé* (avec répartition en papillon, obturation folliculaire et plaques d'atrophie).
2. Forte concentration de cellules de *lupus érythémateux* (quatre ou plus, en deux frottis préparés avec du sang héparinisé, incubés pas plus de deux heures).
3. Signes histologiques de *périartérite noueuse* avec nécrose segmentaire des artères, associée à une infiltration nodulaire leukocytaire, s'étendant périvasculairement et tendant à inclure de nombreux éosinophiles.
4. Faiblesse des muscles du cou, du tronc et du pharynx ou enflure musculaire persistente de la *dermatomyosite*.
5. Sclérodermie établie (non limitée aux doigts).
6. Tableau clinique caractéristique de *rhumatisme polyarticulaire aigu* avec implication articulaire migrante et signes d'endocardite, surtout en présence de nodules sous-cutanés, d'érythème marginé ou de chorée. (Un titre élevé d'antistreptolysine n'éliminera pas le diagnostic d'arthrite rhumatismale.)
7. Tableau clinique caractéristique d'*arthrite goutteuse* avec attaques aigus de tuméfaction, rougeur et douleur surtout soulagés par la colchicine.
8. Tophi.
9. Tableau clinique caractéristique d'*arthrite infectieuse aiguë* d'origine bactérienne ou à virus, avec un foyer aigu d'infection ou en association étroite avec une maladie d'origine infectieuse connue; rhumes; fièvre; atteinte articulaire aiguë, d'abord habituellement migrante (en particulier si l'on trouve des organismes dans le liquide synovial ou si la réponse à la thérapie antibiotique est favorable).
10. *Bacilles de Koch* dans les articulations ou signes histologiques de tuberculose articulaire.
11. Tableau clinique caractéristique de *syndrome de Reiter*, avec urethrite et conjonctivite associées à l'atteinte articulaire aiguë, habituellement migrante au début.
12. Tableau clinique caractéristique de *syndrome épaule-main*, avec atteinte unilatérale de l'épaule et de la main et tuméfaction diffuse de la main, suivie d'atrophie et de contractures.
13. Tableau clinique caractéristique d'*ostéoarthropathie pulmonaire hypertrophique* avec doigts noueux et/ou périostite hypertrophique diaphysaire des os longs, en particulier en présence d'une lésion intrapulmonaire.
14. Tableau clinique caractéristique de *neuro-arthropathie* avec condensation et destruction osseuse des articulations impliquées et signes neurologiques associés.
15. Acide *homogentisique* dans l'urine, décélable grossièrement par alcalinisation.
16. Signes histologiques de *sarcoïde* ou épreuve positive de Kveim.
17. *Myelome multiple* mis en évidence par un accroissement marqué des éléments plasmatiques dans la moelle osseuse, ou présence de la protéine de Bence-Jones dans l'urine.
18. Lésions cutanées caractéristiques de l'*érythème noueux*.
19. *Leucémie* ou *lymphome* avec éléments caractéristiques dans le sang périphérique, la moelle osseuse ou les tissus.
20. Agammaglobulinémie.

Criterios diagnósticos para la artritis reumatoide. Revisión, 1958

ARTRITIS RHEUMATOIDE CLASICA

Este diagnóstico necesita siete de los criterios siguientes. Para satisfacer los criterios de 1 a 5 los signos y síntomas articulares deben ser continuos durante seis semanas al menos. (Cualquiera de los rasgos enumerados bajo el título "EXCLUSIONES" excluye el enfermo de esta categoría.)

1. Rigidez matinal.
2. Movimiento doloroso o sensibilidad en una articulación al menos (observados por un médico).
3. Hinchazón (observada por un médico) de una articulación al menos (espesamiento de tejido blando o líquido, pero no acrecentamineto óseo solo).
4. Hinchazón (observada por un médico) de al menos una otra articulación (cualquier período de tiempo sin síntomas articulares entre las implicaciones de dos articulaciones no debe rebasar tres meses).
5. Hinchazón articular simétrica (observada por un médico) con implicación simultánea de la misma articulación de ambos lados del cuerpo (la implicación bilateral de las articulaciones falangeas medias, metacarpo-falangeas o metatarso-falangeas es aceptable sin simetría absoluta). La implicación de la articulación falangea terminal no satisface este criterio.
6. Nódulos subcutáneos (observados por un médico) sobre prominencias óseas, en la región de los extensores o yuxta-articulares.
7. Alteraciones radiológicas típicas de artritis reumatoide (que deben comprender al menos una decalcificación ósea localizada o predominante en las

articulaciones implicadas y no sólo alteraciones degenerativas)—alteraciones degenerativas no excluyen los casos del grupo de artritis reumatoide.

8. Reacción de aglutinación positiva—demostración del "factor reumatoide" por un método cualquiera que, en dos laboratorios, no ha dado más de un 5 por ciento de resultados positivos en testigos normales; o reacción de aglutinación estreptococcica positiva.
9. Precipitado débil de mucina del líquido sinovial (con trizas y solución turbia).
10. Alteraciones histológicas características de la membrana sinovial, con tres o más rasgos siguientes: hipertrofia vellosa acentuada; proliferación de las células sinoviales superficiales, a menudo con palizada; infiltración marcada por elementos inflamatorios crónicos (con linofocitos o elementos plasmáticos predominantes) con tendencia a formar "nódulos linfoides"; depósito de fibrina compacta superficial o intersticialmente; focos de necrosis celular.
11. Alteraciones histológicas características en los nódulos, comprendiendo focos granulomatosos con zonas centrales de necrosis celular, rodeadas de células proliferantes fijas, y una fibrosis periférica así como infiltración celular inflamatoria crónica, esencialmente perivascular.

Artritis Rheumatoide Definida

Este diagnóstico necesita cinco de los criterios enumerados. Para satisfacer los criterios de 1 a 5 los signos y síntomas articulares deben ser continuos durante seis semanas al menos. (Cualquiera de los rasgos enumerados bajo el título "Exclusiones" excluye el enfermo de esta categoría.)

Artritis Reumatoide Probable

Este diagnóstico necesita tres de los criterios ya enumerados. Para satisfacer uno al menos de los criterios de 1 a 5, los signos y los síntomas articulares deben ser continuos durante seis semanas al menos. (Cualquiera de los rasgos enumerados bajo el título "Exclusiones" excluye el enfermo de esta categoría.)

Artritis Reumatoide Posible

Este diagnóstico necesita dos de los criterios siguientes y la duración total de los síntomas articulares debe ser al menos de tres semanas (cualquiera de los rasgos enumerados bajo el título "Exclusiones" excluye el enfermo de esta categoría):

1. Rigidez matinal.
2. Sensibilidad o movimiento doloroso (observados por un médico) con antecedentes de recurrencia o persistencia durante tres semanas.
3. Antecedentes u observación de hinchazón articular.
4. Nódulos subcutáneos (observados por un médico).
5. Velocidad de sedimentación eritrocitaria aumentada o presencia de proteina C-reactiva.
6. Iritis.

Exclusiones

1. Erupción típica de *lupus eritematoso diseminado* (con distribución en mariposa, obturación folicular y placas de atrofia).
2. Fuerte concentración de células de *lupus eritematoso* (cuatro o más, en dos frotis preparados con sangre heparinizada, incubados en menos de dos horas).
3. Signos histológicos de *periarteritis nodosa* con necrosis segmentaria de las arterias, asociada a una infiltración nodular leucocitaria con extensíon perivascular y con tendencia a incluir numerosos eosinófilos.
4. Debilidad muscular del cuello, del tronco y de la faringe o hinchazón muscular persistente de la *dermatomiositis.*
5. *Esclerodermia* establecida (no limitada a los dedos).
6. Cuadro clínico característico de *reumatismo poliarticular agudo* con implicación articular migratoria y signos de endocarditis, particularmente en presencia de nodulos subcutáneos, de eritema marginato o de corea. (Una cifra alta de antistreptolisina no excluye el diagnóstico de artritis reumatoide.)
7. Un cuadro clínico característico de *artritis gotosa,* con ataques agudos de hinchazón, rubor y dolor en una o más articulaciones, particularmente cuando la colchicina procura un alivio.
8. Tofos.
9. Cuadro clínico característico de *artritis infecciosa aguda* debida a bacterias o virus, con un foco agudo de infección o en asociación estrecha con una enfermedad de origen infeccioso conocido; resfríos: fiebre; y un ataque articular agudo, generalmente migratorio al principio (en particular, cuando se encuentran organismos en el líquido articular o cuando hay respuesta a la terapia antibiótica).
10. *Bacilos tuberculosos* en las articulaciones o signos histológicos de tuberculosis articular.
11. Cuadro clínico característico de *sindrome de Reiter,* con uretritis y conjuntivitis, asociadas a un ataque articular agudo, generalmente migratorio al principio.
12. Cuadro clínico característico de *sindrome hombro-mano,* con implicación unilateral del hombro y de la mano, hinchazón difusa de la mano, seguidas de atrofia y de contracturas.
13. Cuadro clínico característico de *osteo-artropatia pulmonar hipertrófica* con dedos nodosos y/o periostitis hipertrófica diafisaria, en particular en presencia de una lesión intrapulmonar.
14. Cuadro clínico característico de *neuroatropatia* con condensación y destrucción ósea de las articulaciones implicadas y con signos neurológicos asociados.
15. Ácido *homogentisico* en la orina, detectable groseramente por alcalinización.
16. Signos histológicos de *sarcoide* o reacción positiva de Kveim.
17. *Mieloma multiple,* evidenciado por un acrecimiento marcado de elementos plasmáticos en la médula ósea o la proteina de Bence-Jones en la orina.
18. Lesiones cutaneas características de *eritema nodoso.*
19. *Leucemia* o *linfoma* con elementos característicos en la sangre periférica, la medula ósea o los tejidos.
20. Agamaglobulinemia.

Ann. rheum. Dis. (1958), **18**, 54.

HEBERDEN SOCIETY

ANNUAL REPORT, 1958

The President welcomed Mr. M. C. G. Andrews, the successor to Mr. R. V. Howell, Secretary of the Empire Rheumatism Council, as General Secretary of the Society.

He recalled that a special feature of the year had been the joint meeting with the Nederlandse Vereniging van Rheumatologen held in Leyden on the occasion of the Heberden Round, and thanked their Dutch colleagues for the admirable scientific and social programme they had provided on that occasion.

The following new members had been elected:

Ordinary Member: Dr. W. R. M. Alexander.
Associate Members: Dr. J. W. Beattie, Dr. A. Freedman, Dr. G. Will.

The following members resigned during the year:

Dr. D. Hubble, Dr. S. W. Patterson, Dr. F. Wrigley.

The total ordinary membership on January 1, 1959, was 98 and the associate membership twenty.

Activities

At the invitation of Dr. Dudley Hart, the first clinical meeting of the year was held at the Westminster Hospital, on February 14, 1958 (*Annals*, **17**, 251). Papers were presented by Dr. G. D. Kersley (*Bath*), Dr. A. St. J. Dixon (*Post-Graduate Medical School, London*), and Dr. Denis Burley (*Westminster Hospital*); these were followed by demonstrations of patients by members of the Westminster Rheumatism Unit.

On October 11, 1958, a clinical meeting was held at the Stoke Mandeville Hospital, Aylesbury, Bucks, at the invitation of Dr. Alan G. S. Hill (*Annals*, **17**, 446; **18**, 55). Papers were read by Dr. M. S. Good (*Stoke Mandeville*), Drs. A. R. Horler and M. Thompson (*Newcastle-upon-Tyne*), Dr. L. J. Barford (*Redhill*), Drs. A. G. S. Hill and C. L. Greenbury (*Stoke Mandeville*), Dr. W. R. M. Alexander (*Edinburgh*), and Dr. J. F. Buchan (*Holloway*), and a discussion was opened by Dr. H. F. West (*Sheffield*).

The Heberden Oration for 1958 was delivered on December 5 by Dr. Charles Ragan of the College of Physicians and Surgeons, Presbyterian Hospital, New York, at the Wellcome Foundation, London, on "The Role of Hypersensitivity in the Pathogenesis of Rheumatoid Arthritis" (*Annals*, **18**, 1).

The Annual Dinner was held on December 5, by kind permission of the Master, at the Hall of the Worshipful Society of Apothecaries, London. Among the guests present were Sir Geoffrey and Lady Jefferson, Sir Harold and Lady Himsworth, Dr. C. Ragan, and Dr. T. F. Fox.

The Annual General Meeting was held on December 5 and 6 at the Wellcome Foundation, London. At the clinical meeting which followed (*Annals*, **18**, 61), papers were presented by Dr. F. A. Rose (*Manchester*), Drs. I. Porter, M. Lewis, and A. St. J. Dixon (*London*), Drs. S. W. Stanbury, J. Ball, and A. J. Popert (*Manchester*), Prof. E. G. L. Bywaters, Drs. M. Carter, and J. T. Scott (*Taplow*), Dr. J. S. Lawrence (*Manchester*), Dr. R. A. Parkins and Prof. E. G. L. Bywaters (*Taplow*),* and Dr. J. P. Currie (*Glasgow*).

Grant-in-Aid

The Society acknowledged with appreciation the renewal of a grant from the Empire Rheumatism Council.

Library

The Society was indebted to the Ciba Foundation for their kindness in housing the Library at 41 Portland Place, London, W.1, and also for having the large bookcase glazed to render it dustproof.

The Hon. Librarian reported that the Wellcome Trustees had continued to support the library financially, and that he wished to record his personal thanks to Dr. F. N. L. Poynter, Ph.D., Librarian of the Wellcome Historical Library, who had helped in countless ways and had arranged for the books to be cleaned and rebound at regular intervals by his staff. It was intended to publish a new catalogue of the contents of the Library during 1959. The following additions had been made in 1958:

Presented by the Trustees of the Wellcome Medical Foundation:

MISAURUS, P.	The Honour of the Gout. 1720.
STEPHENS, W.	Dolaeus upon the Cure of the Gout by Milk Diet. 1732.
BENNETT, T.	An Essay on the Gout. 1734.
PARKIN, J.	Gout; its Cause, Nature, and Treatment. 2nd ed., 1877.
JEKYLL, J.	A Letter on the Great Utility of Capt. Jekyll's Patent Portable Vapour Bath . . . addressed to Sir Henry Halford, Bt., M.D. 1828.

* This issue, p. 8.

RHYNE, W. Dissertatio de Arthritide. 1783.
RENNIE, A. Observations on Gout. 1825.
REES, G. O. Treatment of Rheumatic Diseases by Lemon Juice. 1849.
STEVENSON, W. A Successful Method of Treating the Gout by Blistering. 1779.

Presented by Prof. Robert Platt, P.R.C.P.:

HEBERDEN, W. Photostat copy of a Note on the Habits of William Harvey communicated to him by Harvey's Great Niece.

Presented by Prof. E. G. L. Bywaters:

SCOTT, J. Surgical Observations on the Treatment of Chronic Inflammation . . . particularly Diseases of the Joints. 1828.

Presented by Dr. W. S. C. Copeman:

MOORE, J. A letter to Dr. Jones on the Composition of the Eau Medicinale d'Husson. 1811.

Presented by Mr. R. V. Howell:

JOHNSON, E. Hydropathy. 1843.

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PROGRAMME FOR 1959

Clinical Meeting at the London Hospital on February 27.

Joint Meeting with the Canadian Rheumatism Association, British Association of Physical Medicine, and North-Western Orthopaedic Club, at the Devonshire Royal Hospital, Buxton, on July 25.

Heberden Round at the Postgraduate Medical School of London, Hammersmith, conducted by Prof. E. G. L. Bywaters.

Heberden Oration, Annual General Meeting, and Dinner on December 4 and 5.

Titles and short programme notes of original communications which Members wish to make to the Society during 1959 should be sent to the Senior Hon. Secretary (Dr. A. St. J. Dixon, M.R.C.P., Department of Medicine, Postgraduate Medical School of London, Hammersmith Hospital, Ducane Road, London, W.12) at least one month before the date of the meeting. Abstracts for publication in the *Annals of the Rheumatic Diseases* (approximately 300 words) should be sent in advance or handed to the secretary at the meeting. Additional meetings will be arranged if necessary.

REPORTS OF MEETINGS

Clinical Meeting.—At a meeting held on October 11, 1958, at the Stoke Mandeville Hospital, Aylesbury, the morning session was devoted to a tour of the Rheumatism Research Centre and to the following demonstrations:

Fluorescent Microscopy, by Dr. D. G. Scott.

Psoriatic Arthritis, by Dr. V. Wright and Prof. S. J. Hartfall.

Intra-Articular Therapy, by Dr. G. W. Chandler, Dr. V. Wright, and Prof. S. J. Hartfall.

Morquio-Brailsford Disease and Keratodermia Blennorrhagica, by Dr. M. S. Good.

Dr. A. G. S. Hill, Dr. M. S. Good, Dr. D. S. Wilkinson, and Mr. G. Platt demonstrated nine patients. These included:

A 72-year-old female with arthritis of the limbs and spine and a rash considered to be keratodermia blennorrhagica in whom Reiter's syndrome was considered to be the possible diagnosis;

A 44-year-old female with systemic sclerosis whose illness had begun with a rash on the hands and feet, Raynaud's attacks, fever, and a polyarthritis involving the hands, shoulders, and neck;

A female, aged 48, with long-standing psoriasis, whose arthritis in the spine, resembling ankylosing spondylitis, had preceded typical changes of psoriatic arthropathy in the limbs by 11 years;

Three patients with rheumatoid arthritis who had undergone surgical procedures: excision of the head

of the radius, bilateral arthroplasty of the knees using stainless steel moulds on the lower ends of the femora, and a McMurray osteotomy of the one hip with very satisfactory results;

A female, aged 38, who had had transient polyarthritis and erythema nodosum associated with more chronic cutaneous lesions of sarcoidosis;

A female, aged 51, who had suffered from psoriasis since childhood and had subsequently developed severe telangiectasia of the face and buccal mucosa with Raynaud's attacks and calcinosis of the fingers considered to represent scleroderma;

A female, aged 32, suffering from Behcet's syndrome who, after 5 years of recurrent buccal ulceration and knee effusions and, later, vaginal discharge, had developed a right hemiparesis which was considered to be a further manifestation of the syndrome.

The demonstration was followed by a discussion of the patients, and at the afternoon session the following communications were delivered:

Temporal or Giant Cell Arteritis. By DR. M. S. GOOD (*Stoke Mandeville*): The twenty patients suffering from temporal arteritis who were studied had been treated in the Royal Buckinghamshire and Associated Hospitals between 1946 and 1957. The illness in these patients, whose ages ranged from 60 to 80 years, had followed an acute or subacute course lasting 3 months to several years; two patients had died, one of them from coronary occlusion.

Headache had been a prominent feature in all cases, tender and thickened temporal arteries in nineteen, constitutional illness, anorexia, and fever in sixteen, pains in the muscles and limbs in ten, and painful stiffness of the jaw and neck and excessive sweating each in nine. Twelve had developed eye involvement, of whom three, not treated by steroids, had become blind within 4 to 5 days; in one patient with eye involvement treated by steroids the vision had improved. The average duration of the disease after biopsy in the eight patients treated by steroids was 2·5 months and in the twelve not so treated 5·4 months. In view of the evidence from this and other reported series that steroid therapy could shorten the illness and prevent blindness, the diagnosis should be confirmed by early biopsy, should be followed by treatment with cortisone 150 to 300 mg. daily for a few days (or the equivalent of prednisolone), and the patient should subsequently receive a lower dosage until symptoms subside and the erythrocyte sedimentation rate falls to normal.

Discussion.—DR. F. D. HART (*London*) cited a patient with temporal arteritis who had received 100 mg. cortisone daily 2 days after the onset of headache, yet had become blind on the sixth day. Other cases were recorded in whom a dose of 100 mg. daily had not prevented blindness; perhaps a higher dosage might have done so. He had seen a number of patients who, after apparent recovery, had diffuse symptoms presumably due to continuous low grade arteritis, not confined to the temporal arteries. These patients were rapidly benefited by steroid therapy.

DR. D. S. WILKINSON (*Stoke Mandeville*) asked Dr. Good to comment on the negative tuberculin test common in this condition.

PROF. E. G. L. BYWATERS (*Taplow*) asked if histamine or alcohol, by causing vasodilatation and increasing pain, might elucidate the diagnosis in doubtful cases.

DR. J. GLYN (*London*) inquired if the disease were improved by locally injected steroids and if it became worse when steroid treatment was withdrawn.

DR. GOOD replied that the patient cited by Dr. Hart had been ill for 3 months before presenting with headache and tender arteries and that cortisone treatment was probably started too late. A few had been seen with tender arteries and an elevated sedimentation rate in whom a definite diagnosis of giant cell arteritis could not be made, since giant cells were not evident on biopsy, but who had been greatly improved by steroid therapy, and he re-emphasized the importance of early treatment with steroids in preventing blindness. He had no information about tuberculin tests or the effects of alcohol or about locally injected steroids in this condition. No exacerbation of the arteritis had been observed during reduction of steroid dosage, but this had been done gradually. The duration of treatment had varied from 14 to 167 days.

Pleural Effusion in Rheumatoid Arthritis. By DR. A. R. HORLER (*introduced*) and DR. M. THOMPSON (*Newcastle-upon-Tyne*): From January, 1956, to December, 1957, 180 patients suffering from rheumatoid arthritis, of whom 52 were men, had been referred to the Department of Physical Medicine at the Royal Victoria Infirmary, Newcastle-upon-Tyne. Pleural effusion had been diagnosed in eight men and one woman, and investigations (including biopsy in three cases) had not revealed any cause for these other than the rheumatoid process. In six of the men no parenchymatous lung lesions were detected and in five of these the development of the effusion was related to the onset of the arthritis. In a series of 180 patients with the same sex distribution and average age, who had musculo-skeletal disorders other than rheumatoid arthritis, only one patient gave a history of pleural effusion and the frequent occurrence of pleurisy and effusion in the rheumatoid patients was the most striking difference between the two groups. It appeared that pleural effusion occurred predominantly in males and was often an inaugural event in the development of the arthritis.

Discussion.—PROF. J. H. KELLGREN (*Manchester*) commented that population studies revealed the sheep cell agglutinating factor to be distributed equally between the sexes although such studies confirmed the clinical experience that peripheral polyarthritis was more prevalent in women. Clinical rheumatoid disease might be different in the male and pleural effusion might be a predominantly male manifestation.

PROF. E. G. L. BYWATERS (*Taplow*) said that he, too, had met such pleural effusions complicating early rheumatoid arthritis, and the question arose whether they were specific to this disease. In his experience,

previously published, there was little evidence for a specific rheumatoid disease of the lung parenchyma, but in that series the *post-mortem* incidence of pleural adhesions in the rheumatoid subjects was about 60 per cent. as against only 30 per cent. in the controls, and he felt there must be some correlation although they had not encountered any appearances specific to rheumatoid pleuritis. Had there been any electrocardiographic evidence of pericarditis in patients with pleurisy? Pericarditis was frequently associated with pleurisy in rheumatoid arthritis; the pericardial histology might occasionally resemble the synovial membrane changes and pleuritis might be of the same nature. His cases had been mainly in females and he wondered whether there was a preponderance of males in Newcastle-upon-Tyne or if there were many miners in the hospital population. He enquired if the pleura was often affected in Caplan's syndrome and whether pleural precede parenchymal lung lesions in that condition.

PROF. KELLGREN agreed that this pleural localization might be conditioned by dust disease in mining populations.

DR. J. BALL (*Manchester*) said that it seemed unlikely that the higher incidence in males could be explicable on an environmental basis. Chronic bronchitis, for example, was more prevalent in hospital patients in Manchester than in Edinburgh, yet a very high incidence of pleural involvement in rheumatoid disease had been reported at autopsy from the Edinburgh district. Local lung lesions, such as chronic bronchitis, therefore, were unlikely to determine the occurrence of rheumatoid changes in the lung.

DR. THOMPSON replied that pericarditis was specifically looked for and that electrocardiographs, which had seemed indicated in four patients, had revealed no evidence of pericarditis. The sex incidence of pleural involvement both in other reported series and in their own was predominantly male, in contrast with the predominantly female incidence of keratoconjunctivitis and conjunctivitis sicca. With regard to occupation, two coal miners in the group with pleural involvement were the only ones with parenchymatous lung changes. Radiography showed that one of them had linear striations unlike pneumoconiosis and that the other had multiple rounded nodular shadows on a background of pneumoconiosis, but on biopsy these did not show the dense aggregations of anthracotic pigment described in the nodules of Caplan's syndrome. They had been unable to find any recorded cases of pleurisy with effusion in Caplan's syndrome, but whether this patient should be regarded as suffering from Caplan's syndrome seemed to be mainly a question of terminology. The other two biopsies had been punch biopsies of the pleura, done to exclude tuberculosis and carcinoma and showed only degeneration of fibrinous material. Chronic bronchitis was present in five of the females and four of the males with rheumatoid arthritis compared with four females and five males in the controls. The prevalence of bronchitis was probably slightly lower than that published for the general population of Newcastle. The incidence of pleural effusion in these patients seemed extraordinarily high and he had sought all possible explanations for it; selection factors might play a part since the patients were received from other clinics in the Royal Victoria Infirmary and might include a higher proportion of examples of more severe and complicated disease.

A Case of Rheumatoid Arthritis with Recurring Pericarditis, L.E. Cells, and Multiple Basal Lung Nodules containing Tubercle Bacilli. By DR. L. J. BARFORD (*Redhill*): A woman, whose mother and only sister had also suffered from the disease, had developed rheumatoid arthritis at the age of 51. From the age of 61 to her death 5 years later she had been treated with either cortisone or prednisolone. For 3 years before death she had had recurrent bouts of fever and pericarditis and systemic lupus erythematosus (S.L.E.) had been suspected, but L.E. cells were not definitely seen until 2 months before death. A chest radiograph at the age of 63 had shown cardiomegaly and basal lung involvement, but tuberculosis had not been suspected.

At autopsy, fibrinous pericarditis with effusion, brown atrophy of the myocardium, and multiple well-defined necrotic nodules containing tubercle bacilli at the lung bases had been found.

Marrow Iron in Rheumatoid Arthritis. By DRS. A. G. S. HILL and C. L. GREENBURY (*Stoke Mandeville*): Specimens of bone marrow from 120 patients with rheumatoid arthritis had been stained by the Prussian blue reaction. Stainable iron was scanty or absent in 56 per cent. of patients and present in excess in 22 per cent.

There was no tendency for either the haemoglobin or mean corpuscular haemoglobin concentration to be higher in patients with stainable iron in the marrow. In cases with excess iron the disease, as judged by the erythrocyte sedimentation rate and the serum concentration of C-reactive protein, tended to be more active; the proportion of patients with active disease and excess iron in the marrow increased with age. Among those with no stainable iron in the marrow there were a number of patients without manifestly active disease but with haemoglobin levels below 75 per cent.; such cases were not encountered among the group with excess iron and their anaemia was taken to be mainly due to iron deficiency.

Patients with anaemia were given 1 g. parenteral iron, usually intravenous saccharated oxide of iron. The rise in haemoglobin after parenteral iron was less consistent in patients with excess iron in the marrow than in those without stainable iron, although a major rise did occur in several instances. In all these cases, however, the rise in haemoglobin coincided with improvement in the disease so that the role of the administered iron was uncertain; the rise might have been spontaneous or related to an action of parenteral iron other than the correction of simple iron deficiency. Excess of iron in the marrow disappeared as the anaemia improved on treatment with steroid hormones. Failure of the haemoglobin to rise after parenteral iron in patients with no stainable marrow was rare and occurred in those with persistently or increasingly active disease.

Discussion.—DR. J. J. R. DUTHIE (*Edinburgh*) reported an investigation in which 26 in-patients with rheumatoid arthritis were each given 5 g. iron intravenously and twenty control patients were given the same basic regime without iron and all were observed for 6 months.

The group given iron showed significantly greater improvement than the controls and the rise in haemoglobin level was associated with a significant fall in the erythrocyte sedimentation rate in all these cases. The rise in haemoglobin following the administration of iron was not related to the initial iron content of the marrow or to the level of iron in the plasma and the improvement in anaemia was mainly due to a rise in the red cell count rather than in the mean corpuscular haemoglobin concentration. The clearance of 200 mg. intravenously injected saccharated oxide of iron from the plasma was just as rapid at the beginning as at the end of the course. He suggested that the effect of intravenous iron was not to supplement a deficiency of marrow iron but to improve the disease process itself. This raised the interesting question whether it was the iron as such that mattered or whether the effect was really due to the administration of a colloidal suspension which was rapidly taken up by the reticulo-endothelial system.

PROF. BYWATERS (*Taplow*) asked if he was right in thinking that the interpretation placed on the results of Dr. Hill's and Dr. Duthie's findings was that the anaemia of rheumatoid arthritis was, as many people suspected, an anaemia of sepsis with failure either to build globin or to incorporate iron in the formation of haemoglobin and that the effect of colloidal substances whether gold or iron was to block the reticulo-endothelial system.

DR. DUTHIE replied that, apart from a short period after the iron injection, the evidence was in favour of a stimulation rather than of a blocking of the reticulo-endothelial system.

DR. HILL re-emphasized the claim for the existence of a group of patients with relatively inactive disease and haemoglobin levels below 75 per cent. in whom iron deficiency was an important but not necessarily the whole cause of the anaemia.

DR. DUTHIE stated that he had also categorized a similar group. All patients with haemoglobin levels below 70 per cent. showed initially the response one would expect with iron deficiency, but if the haemoglobin level rose above 70 per cent. they ran a course similar to those with initial levels above 70 per cent.

DR. GREENBURY felt that, before he accepted the thesis that large doses of intravenous iron might improve anaemia by first improving the disease, he would like to know more about what happened to the control group of patients with iron in their bone marrow who were not given iron.

DR. M. THOMPSON (*Newcastle-on-Tyne*) inquired if the intravenous had any special advantage over the intramuscular route for injection of iron.

DR. DUTHIE thought it had but he was not yet able to do more than state his impression on this.

Elution of the Rheumatoid Agglutination Factor from Bentonite. By DR. W. R. M. ALEXANDER (*Edinburgh*): A method of recovering rheumatoid agglutinating factor from Bentonite particles was described. Particles sensitized with rabbit gamma-globulin were flocculated by exposure to rheumatoid serum. Veronal buffer at a temperature of 56° C. was added to washed flocculates and the protein was then partially eluted from the Bentonite into the buffer. The protein concentration and titre for sensitized sheep erythrocytes in the eluates were measured. The effect of pH on the composition of the eluates was investigated, maximum haemagglutinating activity being present in eluates at pH 8·4.

In order to measure the absolute amounts of human and rabbit globulins in the eluates, the rabbit globulin was labelled with radio-active iodine before the sensitization of the Bentonite particles. It was then shown that the haemagglutinating activity of the eluates varied directly with their content of human protein.

When whole serum was used as the source of rheumatoid agglutinating factor, the ratio of haemagglutinating activity to human protein in the eluates was inconstant over the range of pH 7·6 to 9·2, showing that the eluted protein was not homogenous. When, however, eluates from particles exposed to a euglobulin fraction of rheumatoid serum were examined, the ratio of haemagglutinating activity to protein in the eluates was practically constant over the same range of pH. This suggested that the protein was homogenous and might represent the rheumatoid agglutinating factor, either alone or in combination with a specifically bound globulin. The latter possibility was discussed with reference to the findings of other workers who had concentrated the agglutinating factor by ultracentrifuge techniques.

Discussion.—DR. C. L. GREENBURY (*Stoke Mandeville*) noted that the ratio of protein to sheep cell titre was very high and that, unless Dr. Alexander was using a very insensitive sheep cell test, it was likely that a large amount of the protein was not an active rheumatoid factor.

DR. ALEXANDER replied that he did not know how the sensitivity of his sheep cell test compared with, for example, that of Dr. Greenbury's method. His point was that the ratio of haemagglutinating activity to protein content remained constant. Although the eluates might not be pure agglutinating factor, they might contain a complex of the factor with other proteins of constant composition.

Chloroquine in Rheumatoid Arthritis. By DR. J. F. BUCHAN (*London*): 38 ambulatory patients suffering from rheumatoid arthritis were allowed to take aspirin as required, and were given physiotherapy as indicated, and, after initial assessment, chloroquine sulphate 200-600 mg. (average 470 mg.) daily by mouth. After 2 months, in seventeen of the patients, the chloroquine tablets were replaced by dummy tablets of identical appearance without the knowledge of either the patient or the investigator. The assessments employed were the "activity index" and "articular index" as described by Lansbury (1956).

In the group which continued on chloroquine the activity index was decreased by 26 per cent. at 3 months and by 43 per cent. at 6 months, while in those receiving dummy tablets the index had increased by 21 per cent. at 3 months and 22 per cent. at 6 months. The articular index had decreased by 21 per cent. at 3 months and 38 per cent. at 6 months in those receiving chloroquine, but had increased by 16 per cent. and 12 per cent. respectively in the controls. These differences were statistically significant. The two groups were not matched for sex or severity, the chloroquine group, as judged by

these indices, being initially the more severely affected, but he did not think that the difference in composition of the groups could account for the better results in those continuing on chloroquine, and it was concluded that chloroquine is weakly effective in rheumatoid arthritis. The side-effects observed in these patients were mild and infrequent.

REFERENCE

Lansbury, J. (1956). *Amer. J. med. Sci.*, **232**, 300.

Discussion.—DR. J. RÖTSTEIN (*Minnesota*) stated that the experience at the George Washington Hospital, Washington, D.C., had been that any amelioration of rheumatoid arthritis by chloroquine was evident only after 6 to 8 weeks. Doses in excess of 250 mg. daily frequently caused severe anorexia and depression. Those who had used chloroquine valued it most in disseminated lupus, where concurrent treatment with chloroquine permitted a reduction in dosage of corticosteroids after 6 to 12 months.

DR. O. SAVAGE (*London*) inquired how long it took to derive the Lansbury index for each patient.

DR. A. FREEDMAN (*London*) stated that he had little to add to his published observations on the subject of antimalarials of 3 years ago; he and his colleagues were undertaking a longer long-term controlled therapeutic trial. Long-term therapy with chloroquine seemed beneficial in rheumatoid arthritis and there was a characteristic pattern of improvement on the drug with deterioration when it was withdrawn. Some 30 to 40 per cent. of patients had either to discontinue the drug or reduce the dose to an ineffective level because of toxic effects and this proportion corresponded to the 40 per cent. or so of patients who in long-term studies failed to improve on conservative therapy without chloroquine.

DR. M. S. GOOD (*Stoke Mandeville*) inquired whether Dr. Freedman had used Plaquenil, which in his experience in disseminated lupus seemed to be less toxic.

PROF. KELLGREN inquired whether, as with many other drugs, the less toxic variety was also less effective.

DR. FREEDMAN stated that in his experience the effective dose of Plaquenil was 800 mg. per day and that at this dose toxicity was about as common as with effective doses of chloroquine.

DR. F. BACH (*London*) remarked that, at Moorfields Hospital, where posterior uveitis thought to be due to toxoplasmosis was being treated with antimalarial drugs, the clinical results seemed to be very encouraging.

DR. BUCHAN replied that the estimation of the Lansbury index was not very time-consuming, but without a rubber stamp essential observations could easily be omitted. He had found Plaquenil more toxic than chloroquine.

Clinical Experience with Triamcinolone and Dexamethasone

Opening the discussion on clinical experience with triamcinolone and dexamethasone, DR. H. F. WEST (*Sheffield*) gave a preliminary report on a controlled trial of prednisolone versus triamcinolone, in which 28 rheumatoid arthritic patients who had received prednisolone for at least a year were allocated at random to continue with prednisolone or change to triamcinolone. An analysis of the findings for the first 3 months showed that the prednisolone group had continued to receive a mean dose of 11·3 mg. and that the triamcinolone group had changed from 11 mg. prednisolone to a mean dose of 9 mg. triamcinolone. The latter group had fared slightly better in all the indices of rheumatoid activity. He thought a dose of 9 mg. triamcinolone for a patient of average size to be rather high, and that an even higher dose would lead to the development of fat red face, bull neck, buffalo hump, striae lividarum, and bruising from trivial trauma. Patients receiving prednisolone who slept badly, often slept well on changing to triamcinolone. The fall in appetite that 50 per cent. of the triamcinolone patients experienced was in his opinion more often a disadvantage than an advantage. No significant change in the incidence of dyspepsia was found. It had been reported in the U.S.A. that triamcinolone tended to lower the blood pressure of patients previously on prednisolone, but he had found no change in the mean blood pressure of the triamcinolone group. A further group of fifteen patients who had developed hypertension during prolonged corticosteroid therapy was changed to triamcinolone and their blood pressure was observed for a mean period of 4½ months. There was no significant fall in the blood pressure of the group as a whole. He thought that this divergent finding was due to the fact that in Sheffield they had used a lower dose (8 mg.) than was used by the groups in the U.S.A. He had no report yet to offer concerning the merits of dexamethasone, but he had begun investigations of a rather startling property of the steroid reported by Dr. Bunim's group in Bethesda. It was stated that, although dexamethasone was only six to ten times as effective in rheumatoid arthritis as prednisolone, it was thirty times as potent in suppressing the adrenal. This might mean that a subtherapeutic dose could cause complete adrenal suppression. In a normal subject he had found that after 6 days' therapy 1 mg. dexamethasone did not cause any more adrenal suppression than 10 mg. prednisolone. Dr. Bunim's group had performed acute studies and measured blood levels, whereas West had employed a steady 8-hrly dose and measured the urinary output of total 17 (OH) CS.

DR. F. D. HART (*London*) felt that we should not get anywhere by "rotating the crops" like this. He had hoped from the propaganda put out that there might be less gastric intolerance to triamcinolone, but so far had seen little if any difference. There was less oedema, which was perhaps something in its favour. He had been hoping that triamcinolone might be the answer to psoriatic arthropathy since he had three patients who had done very well when treated with it. However, a dermatological colleague had been dissatisfied with its effects in uncomplicated psoriasis. Dr. Hart doubted if there would be any difference at all in the long-term results. As regards dexamethasone, in initial trials he had switched prednisolone-treated patients tablet for tablet to dexamethasone knowing nothing of the equi-

valent dosages and all the patients had relapsed badly on tablets of 0·4 mg., but on changing to a dosage ratio of 1 : 6 they had all improved again. If the dissociation between its anti-inflammatory and adrenal suppressive effects were confirmed, it might have wider application in the treatment of malignant disease.

DR. G. R. FEARNLEY (*Gloucester*) had used dexamethasone in ten patients over a period of 2 to 3 months. He had also been given optimistic accounts of it by the makers suggesting that its peptic-ulcer-promoting qualities might be much less. Two patients, who had developed ulcers on prednisolone and had healed them in hospital, were given doses of 0·6 mg. and 0·2 mg. of dexamethasone daily; one promptly re-developed a larger ulcer and the other had such intense dyspepsia that the steroid was stopped. Two more patients had developed dyspepsia while taking this steroid. It seemed, from this small group of patients given a small dose, usually 0·6 mg. a day, that although the rheumatoid arthritis could be controlled, peptic ulceration occurred sooner and more severely than with prednisolone.

DR. M. THOMPSON (*Newcastle-on-Tyne*) reported "cross-over" trials of sixteen patients who had been receiving other steroids. Four had had mild dyspepsia with prednisolone and this increased on changing to an equivalent dosage of triamcinolone. Four patients who had previously received steroids other than prednisolone first developed dyspepsia on triamcinolone and one of them had a haematemesis. In a further group of four patients, one had a haematemesis, so that out of twenty patients given triamcinolone eight had severe dyspepsia and two had haematemesis. In all of nine patients with hypertension (which had been present in three cases before the start of steroid therapy), the blood pressure fell after changing to triamcinolone. Two patients, who were euphoric and restless on prednisolone, became less so on triamcinolone. Thus, out of a total of twenty patients, five were considered to be better by and large on triamcinolone for the time being, so that although triamcinolone was not, as the makers suggested, the treatment of choice, it might have a small but useful place in the armamentarium of steroids. Dr. Thompson had also treated fourteen patients with 6-α-methylprednisolone, but in no case had it been found to have any advantage over prednisolone or triamcinolone.

DR. A. FREEDMAN (*London*) inquired if Dr. West knew the explanation of the startling muscle weakness and facial flush observed with triamcinolone.

DR. WEST replied that many patients had muscle weakness to start with and he had not noticed any particular change in this. Some patients did develop intensely red faces and some were dizzy with triamcinolone and it was occasionally necessary to take them off it for these reasons.

DR. J. J. R. DUTHIE (*Edinburgh*) found the rapidly increasing number of available steroids more and more alarming. It was known from previous experience that it took 3 years to assess adequately the long-term effects of treatment, and when one had decided to undertake a trial of one of them it was most disappointing to be told by a pharmacist's traveller "chuck that one out, there is a better one coming along". Experience so far suggested that the fantastic claims for each successive steroid were quite unfounded and that in using them they might well be bringing unknown risks into the care of their patients. The Society should try to protect patients and members should be a little more chary about trying every new steroid. At least half a dozen people had done tentative small trials and he did not think that that approach was going to give any answer at all.

PROF. BYWATERS (*Taplow*) re-emphasized that the essential requirement in the field was a drug which was free from side-effects in a dosage giving adequate anti-inflammatory effects. Many people had felt that the anti-inflammatory and toxic effects were produced by the same mechanism. Some doubted if there could be dissociation between these properties. It had been reported, he thought, that dexamethasone, for the first time among steroids, showed a dissociation between its gluconeogenic and anti-inflammatory properties. This, if substantiated, (and not invalidated by differences in experimental methods of the sort to which Dr. West had drawn attention) was obviously very important.

DR. A. T. RICHARDSON (*London*) referred to two patients, one suffering from polyarteritis nodosa and one from severe asthma, who developed severe and progressive muscle weakness and wasting while taking triamcinolone. Electromyography showed that their terminal nerve fibres and muscle fibres were rotting. Biopsy in one showed widespread hyaline and granular muscle fibre necrosis and much giant cell infiltration. The picture was that of a neuromyositis with, in some cases, marked inflammatory changes.

PROF. BYWATERS pointed out that both patients were suffering from proved or possible polyarteritis nodosa and were, therefore, likely to develop muscle lesions.

DR. FEARNLEY, in reply to Dr. Duthie, agreed that a long period was required fully to evaluate a steroid, but one of these steroids was already being extensively advertised as safe and useful and the other probably would be shortly. The observation by individuals of small series of treated patients was useful in giving warning as to the potentialities of these new drugs.

PROF. KELLGREN said that they had yet to answer the first and most important question, namely, was the use of prednisone or prednisolone in safe dosage on a long-term basis really an advantage in rheumatoid arthritis. Until this question had been answered, large-scale controlled trials of other steroids hardly appeared justified. He agreed with Dr. Fearnley, however, that it was important that someone should get a little personal experience of these drugs as they came out. Somebody had to do it and he was always grateful to his colleagues who did so. But the testing of these new steroids as they came out should not block facilities for testing other agents or interfere with other important studies.

PROF. KELLGREN, in closing the meeting, expressed the thanks of members to Dr. Hill and all the other members of the staff of the hospital who had contributed so much to a memorable and thoroughly enjoyable meeting.

Annual General Meeting.—At the Annual General Meeting held at the Wellcome Foundation, London, on December 5 and 6, 1958, with the president, Professor J. H. Kellgren, in the chair, the following communications* were delivered:

Some Features of the Biochemistry of Sulphated Substances. By DR. F. A. ROSE (*introduced, Manchester*).

The study of sulphate metabolism has become popular and important during recent years but, despite the significant progress made by several groups of workers, knowledge of this subject remains limited, and the physiological role of sulphate esters and associated enzyme systems is still largely theoretical.

Sulphated polysaccharides have occupied a prominent position in this field because of their significance as connective tissue constituents. However, other lesser known sulphate esters, *e.g.* sulphates of simple carbohydrates (glycosulphates), phenols (arylsulphates), aliphatic alcohols (alkylsulphates), amino compounds (sulphamates), and of steroids, have also received considerable attention. Some occur naturally while others are purely synthetic compounds; in this connexion many interesting problems arise. For instance, the discovery of tyrosine-*o*-sulphate in fibrinogen (Bettelheim, 1954) has suggested a more widespread distribution of the arylsulphates, which hitherto were known to occur naturally only in urine, tyrosine-*o*-sulphate being also a natural constituent of urine (Tallan, Bella, Stein, and Moore, 1955). The natural occurrence of simple carbohydrate sulphates has not yet been observed, although the corresponding phosphate esters are well known.

Sulphate hydrolysing enzymes, the sulphatases, have also been the subject of considerable investigation. A wide distribution of these enzymes, specific for the various types of sulphates, has been demonstrated (Dodgson and Spencer, 1957), *e.g.* chondrosulphatase in putrefactive bacteria, marine molluscs, and possibly mammals; glycosulphatase, in mammals, bacteria, fungi, and molluscs; arylsulphatase in mammals, birds, insects, bacteria, fungi, molluscs, and plants; steroid sulphatase in marine and terrestrial molluscs and possibly in mammals. Many problems relating to the physiological function of these enzymes remain unsolved since, in numerous instances, the distribution of the enzymes and their probable natural substrates seems anomalous; for the widely distributed arylsulphatases, for example, the natural substrates are unknown.

Ester sulphate formation has been shown by Lipmann (1958) to take place through the intermediate formation of a high energy sulphate, 3^1-phosphoadenosine-5^1-phosphosulphate ("active sulphate"). The process involves two reactions:

(*a*) formation of active sulphate from ATP and inorganic sulphate;

(*b*) transfer of the sulphate group from "active sulphate" to suitable acceptors, such as phenols, carbohydrates, and steroids.

The results of these diverse studies indicate that the metabolism of sulphate esters of different types and locations may be related through enzyme systems and reactions not yet recognized. Moreover, it seems likely that a search for other naturally occurring sulphate esters would be rewarding.

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Discussion.—DR. G. LOEWI (*Taplow*): Differentiation of the various types of sulphated polysaccharides can be of practical value in the elucidation of a disease process. Meyer has identified three types of chondroitin sulphate: "A", "B", and "C". Chondroitin sulphate "B" is excreted in large amounts in the urine by gargoyles, and this is the first metabolic abnormality that we know of in the mucopolysaccharide field. I have recently been attempting to isolate the sulphated polysaccharide excreted in the urine by patients with rheumatoid arthritis. This substance is probably chondroitin sulphate "A". Knowledge such as this may help one to trace the origin of an excreted polysaccharide, since different tissues contain different patterns of polysaccharide. Thus chondroitin sulphate "A" might be derived from bone or cartilage.

My second point is concerned with the sulphatases described for us by the speaker. One usually thinks of these as hydrolytic enzymes. I think it would be worth while remembering that these and similar enzymes might well be concerned in synthetic systems. Perhaps I should add that I have tried several systems in an effort, which has so far been unsuccessful, to demonstrate synthesis of glucuronides in the presence of the enzyme β-glucuronidase.

DR. H. F. WEST (*Sheffield*): I should like to ask Dr. Rose two questions. First, we are interested these days in the role of steroids as co-enzymes moderating transhydrogenase reactions. In the reaction you have mentioned, what co-factors are concerned in the transfer of activated sulphate? Secondly, you mentioned the possibility that steroid sulphatases may be active in tissues. Have you any evidence that this is so?

DR. ROSE: In connexion with the first point, in the general overall sulphation process, the main requirements are ATP, which is of course a main reactant, and magnesium.

DR. H. F. WEST: What are the co-factors in the enzymatic transfer of the sulphate?

DR. ROSE: It is difficult to say exactly what is involved at this stage, since the individual reactions are not yet fully worked out. The two parts of the process were

* Papers which it is hoped will be the subject of a fuller communication in the *Annals of Rheumatic Diseases* are here reported in summary only.

separated only comparatively recently, but quite a lot of work is now being done on these systems. Recently it has been suggested that this reaction is influenced by the nucleotide formed in the reaction, and by -SH compounds.

In answer to the second question, this was just a theory adopted to try to explain the possible physiological functions of the enzymes and the sulphates, but it has not yet been substantiated and is open to criticism.

Salicylate Therapy and Faecal Blood Loss (in Summary). By DR. I. H. PORTER (*introduced*), DR. M. LEWIS (*introduced*), and DR. A. ST. J. DIXON (*Hammersmith*).

This paper is concerned with the relationship between salicylate therapy and intestinal bleeding. At a recent meeting of the Heberden Society at Leyden, Stubbé (1958) demonstrated that occult bleeding, as tested quantitatively by the Benzidine method, occurred in 70 per cent. of 180 people taking aspirin. As salicylates are the sheet-anchor of treatment in rheumatology, we thought it important to substantiate this claim by a sensitive and more accurate method.

The method consists of tagging a sample of the patient's red cells with ^{51}Cr, returning them to the circulation, and measuring the radioactivity of the stools. Owen, Bollman, and Grindlay (1954) showed that 90 per cent. of chromium tagged red cells introduced into the stomach or duodenum could be recovered in the faeces, and Roche, Perez-Gimenez, Layrisse, and di Prisco (1957) that negligible amounts of circulating tagged red cells are excreted in the faeces in normal individuals. The present method (details of which will be published later) can detect as little as 1 ml. blood in a 24-hr sample of faeces. The counting system has an accuracy of 5 per cent. and recovery experiments after tagged blood has been fed to animals and volunteers, have been satisfactory.

The first part of the study concerned eleven patients routinely admitted to the rheumatology wards at Hammersmith Hospital, in whom anaemia was not a feature, who had no symptoms or signs of peptic ulcer and who showed no evidence of bleeding from other sites in the intestinal tract. Ten had rheumatoid arthritis and one degenerative joint disease. All were on a normal ward diet, stools were collected daily, being tested for total radioactivity and (on a spot sample) for occult blood by the *o*-toluidine method. Therapy was given in 5-day blocks, as follows: Days 0-5, previous therapy; Days 6-10, aspirin; Days 11-15, enteric-coated sodium salicylate; Days 16-20, aspirin; Days 20-25, calcium aspirin. The dose was 1 g. four times a day.

The chemical method showed occult blood in 72 per cent. of stools for the aspirin or calcium aspirin periods, but in only 25 per cent. of the stools for the enteric-coated sodium salicylate periods.

The radioactive method, in contrast, showed that *every* patient bled when taking aspirin or calcium aspirin (there was no difference between these preparations), but when the patients changed to enteric-coated sodium salicylate the blood loss became less or disappeared. The difference between the two methods for detecting blood is probably due to sampling errors and dietary haemoglobin. A total of 208 stool samples tested by one observer gave the following comparison:

Chemical Method	Radioactive Method	
	0–2 ml. blood	2–20 ml. blood
Positive	60 per cent	73 per cent.
Negative	40 per cent.	27 per cent.

Thus, under these circumstances, the chemical method is quite unreliable for small amounts of blood ($<$ 2 ml.) although it gives a better correlation for larger volumes.

Results were reproducible and thus we have confirmed that aspirin and its calcium salt cause intestinal bleeding. However, in these patients (who were not anaemic) the loss was small, usually less than 5 ml. per day, and of doubtful clinical significance.

In our second experiment we investigated iron-deficiency anaemia of unknown cause in four patients taking no other medicine than aspirin, who showed positive chemical tests for occult blood. In all four patients much larger losses of blood were found; in one up to 60 ml. per day was detected. Again the losses were reproducible, and ceased or were markedly reduced (and the anaemia improved) when the patients were taken off aspirin or calcium aspirin. There are several possible explanations of this bleeding. Allergy, increased gastric acidity, disturbances of coagulation mechanisms, or the increased capillary fragility of rheumatoid arthritis are all unlikely explanations, as we have observed the phenomenon in the absence of these factors. Local irritation of the stomach is a more likely explanation and has indeed been observed by Douthwaite and Lintott (1938) and by Muir and Cossar (1955).

The minor degrees of bleeding we observed in patients without anaemia, although of no immediate importance, could, after months or years, eventually lead to depletion of iron stores and iron deficiency anaemia. This would be most likely to occur in women who were menstruating.

The technique itself is proving valuable in the assessment of other drugs and hormones suspected of producing anaemia or gastro-intestinal bleeding.

We may conclude that:

(1) All our patients in this series bled when taking aspirin or calcium aspirin.

(2) These losses were small and of doubtful significance in eleven routine cases without anaemia.

(3) In an unexplained iron deficiency anaemia, aspirin should be thought of as a possible cause.

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Discussion.—DR. DUDLEY HART (*Westminster Hospital*): Were the enteric-coated sodium salicylate tablets actually absorbed?

DR. PORTER: We did not do the blood salicylate levels, but those patients who had pain got relief from enteric-coated sodium salicylate tablets, and we never saw the tablets in the stools.

DR. J. J. R. DUTHIE (*Edinburgh*): It is reassuring to hear that, in the majority of cases studied, blood loss during the administration of aspirin was relatively insignificant. Our own studies of anaemia in rheumatoid arthritis do not suggest that iron deficiency plays a direct role in more than a small proportion of cases. This sort of information tends to reach the public in a distorted form, and may produce exaggerated fears as to the dangers of the continuous administration of aspirin, the most valuable single remedy for the control of symptoms in rheumatoid arthritis. We may find it increasingly difficult to persuade our patients to continue with adequate doses of salicylates. In order to ascertain if salicylates were really a cause of anaemia in practice, we reviewed the records of those patients who had been continuously on aspirin or calcium aspirin since 1954. The data were adequate in 47 cases of rheumatoid arthritis. The mean initial haemoglobin in this group was 79·2 per cent. (S.D. ±8·38). The final haemoglobin was 87·2 per cent. (S.D. ±10·48). It is true that thirty of these 47 cases had received iron in one form or another during these 4 years, often in the absence of a significant degree of anaemia. The prescription of iron for patients with rheumatoid arthritis is common in general practice. These results do not suggest that salicylates in the doses commonly in use are a significant cause of anaemia due to blood loss.

DR. C. RAGAN (*New York*): Is there any relationship between dosage and blood loss?

DR. PORTER: We used a standard dose. We intend to investigate the effect of varying the dose.

THE PRESIDENT: I think the paper we heard at the meeting in Holland showed that in normal individuals the dosage mattered very little, even quite a low dose induced the same effect; that was shown by ordinary clinical techniques. Do you remember that, Professor Bywaters?

PROF. E. G. L. BYWATERS (*London*): Yes, I think that is correct. This is obviously going to be a useful screening method for new steroids and other suppressive agents. The usefulness of these substances depends upon the ratio between the therapeutic dose and the toxic dose. With regard to gastric erosion we need to know, for instance, whether sodium salicylate is different from aspirin for the same therapeutic effect, whether enteric coating is itself valuable, or whether the important factor is what differences alkalis make and how the new steroids differ from the old ones. There are numerous other points we are now investigating with this technique: I think Dr. Porter and his colleagues have made a promising start and we should learn a good deal more on this subject.

DR. J. G. SCLATER (*Edinburgh*): Is there any evidence whereabouts in the alimentary tract the haemorrhage is occurring?

DR. PORTER: We have no personal observation on that. Miss Muir has made some observations after gastrectomy and Douthwaite has observed it at gastroscopy after aspirin.

PROF. E. G. L. BYWATERS: One of the speakers in Holland referred to Dr. Douthwaite's paper in which gastroscopy showed similar local inflammation after eating mustard as after aspirin. The average stomach is a very tolerant organ and aspirin is just another one of numerous daily insults.

DR. L. J. BARFORD (*Redhill*): Dr. Porter has told us that aspirin and "Disprin" both give rise to this bleeding, but I wonder if he has any evidence whether or not haemorrhage will still take place if one gives an alkali with the aspirin.

DR. PORTER: We have not added alkalis nor were the aspirins given straight after meals, but we are going into these problems.

PROF. E. G. L. BYWATERS: Since the stomach juice is a dilute solution of hydrochloric acid, it seems possible that there is less difference between calcium aspirin and the ordinary aspirin *in vivo* than *in vitro*. If you dissolve calcium aspirin in water and pour it into dilute hydrochloric solution, you get a cloudy crystalline precipitate.

A SPEAKER: Would it follow from the paper that if one were investigating a patient with blood in the stools that it would be sufficient to exclude aspirin 48 hours previously?

DR. PORTER: No. A few patients have shown bleeding for 10 or 15 days although most had cleared up by 3 days. 48 hours would be too soon.

DR. A. J. POPERT (*Manchester*): I should like to know how you achieve the regular daily collection of 24-hr stools. What happens if the patients get constipated?

DR. PORTER: There were gaps in the collections, as you will have noticed, which were indicated by blank spots on the charts. I agree, it is quite a problem, as patients tend to become constipated in hospital.

DR. DUDLEY HART: Patients do get gastritis with the iron preparations and it would be interesting to see what happens with some of these.

Simulation of Rheumatic Disorders by Metabolic Bone Diseases. By DR. S. W. STANBURY (*introduced*), DR. A. J. POPERT, and DR. J. BALL (*Manchester*).

Osteomalacia is a disease sometimes regarded as showing itself only in some parts of Asia and the Middle East. In fact it is by no means an uncommon disease in Great Britain, and by giving rise to diffuse pain in the locomotor system, may suggest the presence of some rheumatic disorder. It can complicate renal disease, both in the specific tubular disorders and, more often, in chronic uraemia; it should be borne in mind as the possible cause for pain developing in patients with a variety of intestinal and hepatic diseases; it occurs as the important clinical manifestation of a group of hereditary metabolic disorders. Its supposed rarity partly reflects the clinician's inability to diagnose it, with the result that the patient's symptoms, although usually described accurately, tend to be dismissed as "fibrositis", "neuritis", "osteo-arthritis", "muscular rheumatism", and even often as psychoneurotic or hysterical.

Pain in osteomalacia occurs most commonly in the back, the groins, and the upper part of the thighs; but it can be felt anywhere in the limbs or in the thorax, where it may simulate pleurisy. Characteristically it is intensified by movement and relieved by rest in bed. Walking, climbing stairs, or simultaneous flexion of knees and hips when bearing the body-weight are especially painful. [A motion film was projected to illustrate the discrepancy between the painless active movement of the leg joints in recumbency and the pain and disability produced by weight-bearing.] The patient walks with short, hesitant steps and a rolling gait which are almost diagnostic, although often construed as hysterical. Routine physical examination is often unrewarding, but some patients exhibit osseous tenderness and others the stigmata of previous rickets. A presumptive clinical diagnosis is facilitated by seeing the patient deliberately attempt those movements which commonly produce pain; final diagnostic proof is provided by demonstration of the wide osteoid seams in biopsy specimens of undecalcified bone.

Radiography may reveal an apparently normal skeleton or bones of reduced density, but the important diagnostic feature is the presence of multiple fractures. Since individual fractures may not produce symptoms, they must be specifically sought at their sites of elective occurrence in the pelvis, ribs, femoral necks, scapulae, and shafts of the long bones.

A particular diagnostic problem is created by the frequent early limitation of pain to the back. Physical examination and the radiographic appearances of the spine may be normal, or there may be a diffuse or banded sclerosis of the vertebral bodies. This paradoxical appearance of vertebral osteosclerosis should suggest the diagnosis of osteomalacia or of hyperparathyroidism. In a small group of adult patients with "familial vitamin D resistance or renal hypophosphataemia" and chronic osteomalacia, the spinal changes had simulated ankylosing spondylitis. Secondary bone proliferation around apophyseal joints, ossification of spinal ligaments, and complete or partial obliteration of the sacro-iliac joints had been seen. In some of these patients, the presence of femoral bowing and osseous density had led to an earlier misdiagnosis of Paget's disease. These patients, as do all other cases of osteomalacia, responded clinically and biochemically to the appropriate large doses of vitamin D.

Discussion.—DR. A. ST. J. DIXON (*London*): I should like to show a picture of a 50-year-old female dwarf with metabolic bone disease. She had previously been diagnosed as a possible case of achondroplasia. She came under our care because she had developed classical rheumatoid arthritis; that is, she had a peripheral polyarthritis, subcutaneous nodules (confirmed histologically), a positive D.A.T., and subchondral erosions of bone seen on *x* ray. However, she gave a history of rickets as a child and there were features of her pain, such as thoracic backache, worse at night, which suggested that she still had active osteomalacia. I admitted her for bone biopsy, and metabolic studies were kindly done by Professor Russell Fraser. She did indeed have active osteomalacia, which was helped by calciferol. The history and investigations pointed to impaired fat absorption as the underlying cause. In this case rheumatic disease tended to mask the symptoms of a treatable metabolic bone disease.

PROF. E. G. L. BYWATERS (*Taplow*): Metabolic conditions of bone not infrequently present at Rheumatism Units, and since Dr. Stanbury in his fascinating account has confined himself to osteomalacia, I might perhaps mention hyper-parathyroidism. We have been interested in that and in other bone conditions where there is cellular infiltration, *e.g.* hypercholesterolaemia due to biliary cirrhosis, where infiltration of bone will produce curious and usually symptomless changes in the neighbourhood of the joints and sometimes even collapse with secondary arthritis. In the last 10 years we have seen six patients with hyper-parathyroidism at Taplow and Hammersmith, in whom we have seen the curious phenomenon of calcium deposition on articular cartilage. This has been observed as an idiopathic phenomenon, but not hitherto I believe in hyper-parathyroidism. It may involve almost all joints.

The spine in this condition shows collapse of vertebrae which is usually productive of symptoms. There may also be dislocations in the spine perhaps due to softening of tendon and ligament attachments. The most interesting lesions, however, are those in the neighbourhood of joints, and one woman, for instance, showed bilateral changes in the humerus, consisting of apparent cysts immediately beneath the cartilage with apparent loss of cartilage. The bony structure is sometimes completely destroyed as could be seen in the left thumb of another patient, a woman aged 74, in which it extended up to the cartilage of the joint space; yet immediately after the removal of the parathyroid adenoma there was reformation of the bone with deformity of the articular surface. This would conduce to early degenerative changes and symptoms.

Sometimes there are curious changes in the subcartilaginous bone, resembling the changes of rheumatoid arthritis. In a case of hyper-parathyroidism, one could see the apparent filling after operation of what had previously appeared to be erosions in the metacarpal heads.

In other patients the carpus appears to be involved, as in another woman aged 65, in whom the calcium, phosphorus, and phosphatase reverted to normal after the removal of a parathyroid adenoma. Between the ages of 60 and 65 there was collapse of the carpus as in rheumatoid arthritis, and the bones became squeezed together. She has lately developed an effusion in both knees and we have one reading of a raised erythrocyte sedimentation rate. In the knee there was some collapse of the cartilage, and calcification could be seen in the meniscus.

This appearance may give rise to considerable difficulty: we have recently had a patient at Hammersmith who was thought, on clinical examination, to have rheumatoid arthritis; there was effusion and pain in the knees with limitation of movement and a raised erythrocyte sedimentation rate. *X* rays showed classical hyperparathyroid changes and we did not really know whether this was rheumatoid arthritis plus hyper-parathyroidism or hyper-parathyroidism only with secondary degenerative changes. The lateral view of the knees appeared to show erosions at the back of the femoral condyle on the right and severe changes in the femoral surface of the left patella, with some flattening of the patella.

Another patient of Prof. Russell Fraser's showed the

same type of changes in the patella but not in the femoral condyle.

PROF. RUSSELL FRASER (*Hammersmith*): I do not know that I can contribute very much to the discussion; most of the points have been brought out very well. One point I should like to make is that it was once a puzzling thing in myxoedema that the erythrocyte sedimentation rate was commonly very high; no doubt that is connected with its common basis in Hashimoto's disease or lymphadenoid goitre. I do not think we need always take it as an indication of inflammatory disease.

Another question is how may patients with apparent joint disease be distinguished from patients with truly primary joint disease; in this the biochemistry of the serum will very often give a clue. I suppose that one should always look for causes a little more widely than merely in the joints themselves. The *x* rays which Prof. Bywaters showed suggest some of the circumstances when it would be reasonable to estimate the serum calcium in the rheumatoid patient. When there is any doubt after that, we have found it useful to make a measurement of the rate of calcium turnover through the bone; because there is a rapid turnover of calcium in and out of the bone in most of these bone conditions, which may be confused. No doubt the important cases will be recognized if the standard biochemical assessments are made in doubtful cases, *i.e.* fasting serum phosphate, blood calcium and blood urea.

Rose-Waaler Titre in Still's Disease (in Summary). By PROF. E. G. L. BYWATERS, DR. M. E. CARTER (*introduced*), and DR. F. E. T. SCOTT (*Taplow*).

The Rose-Waaler test (D.A.T.) was studied in a series of 142 children with Still's disease who were under 16 years at the time of onset of the disease. The patients, admitted to the Rheumatism Research Unit at Taplow, were followed for a minimum of 4 years and a maximum of 10, and the mean number of D.A.T.s done per patient was 9·5.

The overall D.A.T. results on the series showed that 13·4 per cent. of patients were sero-positive at the first test; 45 per cent. had at least one positive test, and 19·7 per cent. had two or more.

There was a tendency for patients with the largest number of positive D.A.T.s to fall in the older age group, and a tendency for males to be more frequently D.A.T.-positive than females.

There was much variation of D.A.T. titre during the course of the disease—some patients being initially sero-positive and changing to negative, or *vice versa*—but there was a general tendency for the test to become negative with duration of disease, and this was slightly more marked in "early" cases (those seen within one year of onset).

The average time taken to convert from positive to negative or *vice versa* was 2 to 3 years. There was little tendency for the D.A.T. to convert to positive in the older groups, but the series is small and the period of observation short.

There was no very close correlation between sero-positivity and disease activity even in those who showed a number of positive results, and the only clinical feature correlated with a positive result was the presence of nodules.

Discussion.—DR. C. RAGAN (*New York*): I should like to make two comments. One is that in our group at the Presbyterian Hospital, forward-looking studies such as this are difficult to carry out and I congratulate Dr. Carter and her group. We have recently carried out a retrospective study of Still's disease, and in a group of 119 patients the D.A.T. was positive in about 10 per cent. We are impressed with the fact that those with sustained disease are, as a group, more likely to have a positive test, although there are exceptions who have a negative titre throughout the course of the disease. Alternatively, patients with a positive agglutination may have intermittent disease or enjoy complete remission.

Using our type of differential agglutination test, which is somewhat similar to that described by Dr. Carter, we have been unable to get consistent results from year to year, even from hour to hour, on the same serum and I think this may be related to batch differences in the biological reagents employed. By using the F II modification of the differential agglutination test, we can by internal standardization get repeatable results from year to year on the same patients and on the same samples of serum. Thus this is a suitable standard technique which can be used to follow a patient for a long time. However, it shows some loss of specificity compared with the original sheep cell agglutination test.

DR. J. BALL (*Manchester*): I should like to say that variations in sheep cells may not be so much to blame as some have suggested. It has been our experience, using very strict criteria for internal control of the tests, that only on very rare occasions, perhaps once in two years, do we get obviously poor blood from our suppliers which causes anomalous results. I think it is more likely that titre variations arise from using different batches of haemolysin, especially if some arbitrary titre such as agglutinin or haemolysin titre is used to determine the dilution of this reagent.

The paper is extremely instructive because we have seen relatively few patients below the age of 16 and positive tests among these seemed too infrequent to justify paediatricians using this test at all; perhaps this is a false impression.

Finally, I should like to ask a question about the actual distribution of titres within the group as a whole. Because of the relatively poor serological response in the whole group the titre distribution curve might be different from what one finds in adult disease; I imagine a higher proportion of tests fall in the lower titre range—the titre distribution curve would be shifted to the left and thus a relatively large number of titres would straddle the borderline defining positive and negative tests. In practice this might make the test less satisfactory in the under 16 age group than in adults.

DR. A. G. S. HILL (*Stoke Mandeville*): Has anybody any experience of D.A.T. in adult patients in whom the rheumatoid arthritis started before the age of 16 years? We have had four such patients and in all of them the tests were negative even when they had passed that age. This seems to be interesting and I imagine this series will be followed through into adult life, perhaps for a long time; one does see some of these patients in adult life and I wondered whether any one knew the answer.

DR. C. RAGAN: A third of our patients are over 21 now; this is the 13th year since the original tests.

DR. SCOTT: In answer to Dr. Ball's question on the

distribution of titres, it was indeed our finding that the titres in the first decade age group were near to the border line, in the second decade more were positive with a higher titre, and this trend continued up into the sixth decade when patients who were positive were usually positive at a very high titre, many of them round about 1 : 128 or higher, whereas at a lower age it was 1 : 32 and 1 : 64. This can account for some of the variability in the results which were quoted, because in the lower age groups a one-tube variation in titre might make all the difference between positive and negative.

THE PRESIDENT: That raises an important question, whether the titre distribution in the age groups should not be taken into account in the positivity and negativity. There may be different titre distributions in the general population in different age groups. I do not think we have really considered this possibility.

Rheumatic Disease in an Urban Population. By DR. J. S. LAWRENCE (*Manchester*).

In a random sample of the adult population of the town of Leigh, Lancs., submitted to clinical and radiological investigation of the skeletal system and a sheep cell agglutination test, rheumatic complaints were encountered in 31 per cent. of males and 41 per cent. of females. Some 12 per cent. of males and 8 per cent. of females gave a history of being incapacitated by rheumatic trouble for 3 months or more.

The most frequent sites of pain in both sexes were the low back or thighs (corresponding to the segmental areas of referred pain D.12 to L.2), the knees, and the shoulders and arms (segments C.5 to D.2). Physical signs were encountered mainly in the spine and knees.

The most frequent radiological diagnosis in both sexes was intervertebral disk degeneration which, in moderate or severe grade, was encountered in 30 per cent. of males and 33 per cent. of females. Moderate or severe osteo-arthrosis was present in 21 per cent. of males and 23 per cent. of females. Rheumatoid arthritis, spondylitis, Paget's disease, generalized osteoporosis, and osteochondritis were all present in less than 5 per cent.

The sheep cell agglutination test was positive in 6 per cent. of either sex.

Of 134 who had lost work through low back and thigh pain, 67 had lumbar disk degeneration, seventeen had osteo-arthrosis of the lumbar apophyseal joints, twelve had evidence of rheumatoid arthritis, six of disk prolapse, three of spondylitis, and one of generalized osteoporosis. In 33 no cause was found.

Of 76 who had lost work through knee pain, 32 had osteo-arthrosis of the knees, 21 had evidence of rheumatoid arthritis, thirteen had a history of past polyarthritis, two synovitis, and one gout, and two were considered to be non-rheumatic. In five there was no objective evidence of disease.

Of 68 who had lost work through cervico-brachial pain, 28 had cervical disk degeneration, 27 had evidence of rheumatoid arthritis, nine osteo-arthrosis of the cervical apophyseal joints, two spondylitis, one rheumatic fever, and one disk prolapse, and in eight there was no associated evidence of disease.

Of 44 who had lost work through shoulder pain, eighteen had evidence of rheumatoid arthritis, seven had cervical disk degeneration, four osteo-arthrosis, three rheumatic fever, three were thought to have had capsulitis, and in thirteen no objective cause was found.

Disappearance of Intracutaneously Injected Congo Red Dye. By DR. R. A. PARKINS (*introduced*) and PROF. E. G. L. BYWATERS (*Hammersmith*).

This paper and the discussion thereon will be found on p. 8 of this issue of the *Annals*.

Evaluation of Anti-Inflammatory Compounds. By DR. J. P. CURRIE (*Glasgow*).

The "analgesic-antipyretic" group of drugs has been under investigation now for about a hundred years. In spite of the application of new techniques and standards of measurement, the early impression that these drugs were specially effective in relieving "rheumatic" or musculo-skeletal and joint pain has remained established.

The more recent application of C_{21} steroid compounds to the treatment of rheumatic disease naturally led to efforts to demonstrate some common mode of action. All of these efforts have failed, yet these two quite dissimilar groups of compounds continue to produce some very similar actions in both experimental animals and humans. For the purpose of this short communication, I wish to confine myself to only one, *viz.* the inhibition of the normal reaction to injury.

In experimental animal work—especially with small animals such as rats and guinea-pigs—the most widely used method is the study of the formation and development of oedema in traumatized joints and limbs. This procedure has the advantage of being comparatively simple, accurate, and controllable. The trauma is supplied by introducing into either a paw, or a joint, egg albumen or a suspension of Kaolin. A further method involves the study of the erythema, vesication, and desquamation, resulting from exposure of the skin to ultra-violet light.

In screening compounds for potential anti-inflammatory action, a battery of these tests has been employed, along with tests of "central" and "peripheral" analgesic potency, antipyretic effect, water-retaining effect, and anti-histaminic effect, both in rabbits and in guinea-pigs. Results for some of the compounds tested are summarized in the Table, along with an estimate of the potency of action in rheumatoid arthritis. From these results, the following conclusions seem justified:

(1) The effectiveness of the trial compounds varies with the type of trauma used.

(2) Compounds exhibit different pharmacological effects—at least quantitatively—in different species.

(3) Experimental animal results of this kind appear to bear little relationship to human therapeutic value.

(4) The screening methods presently employed, seem to be missing some essential factor relating to the pharmacodynamics of these compounds.

TABLE

Compound	Type	Results									
		Experimental									Clinical (In Rheumatoid Polyarthritis)
		* Egg Albumen Oedema (per cent.)	* Kaolin Oedema (per cent.)	† Ultra-Violet Light Erythema	† Anti-pyretic Action	† Analgesic Effect		† Anti-Histaminic Effect		† Water Retention	
						Central	Peripheral	Rabbit	Guinea-Pig		
Ro 1/9106	Pyridazone	−20	−20	−1	−1·5	+2	0	+	0	4	Central nausea and vomiting with small doses Evaluation impossible
G. 13871	Pyrazol	−15	−20	−3	−1·0	0	+3	+	+	3	Markedly analgesic ? Anti-phlogistic
Ro 4/0688	Pyrimidine	−1	−15	−4	−0·25	0	0	+	0	0	Ineffective
Ro 5/0162	Thio-urea	−20	−30	−2	0	0	+3	+	0	0	,,
Ro 4/1318	Isoquinolin	−15	−10	−3	−1·0	0	+1	0	+	3	,,
G. 25731	Pyrazol	−10	−35	0	−0·5	+3	0	+	+	1	,,
G. 26550	Pyrazol	−15	−10	0	−3·0	0	0	0	0	0	,,
G. 29330	Glyoxaline	−15	−15	−3	0	+1	+1	0	+	0	,,
Ro 2/5002	Isonicotinyl hydrazide	−20	−20	−3	−1·0	0	+2	0	+	0	,,
Sk/1	Salicylate	−15	−15	0	−3·0	+0·5	0	+	0	0	Moderate analgesic activity
Ro 4/0259	Triazol	−15	−20	−2	0	0	+2	+	0	0	Negative

* Expressed as percentage weight reduction compared with controls.
† Expressed as arbitrary grades.

All this work, though largely negative, is not quite useless, for, as frequently happens in planned research, certain incidental findings have proved valuable.

Kuzell first showed that a Pyrazol, phenylbutazone, was effective in terminating the acute attack of gout, and claimed that, in addition, it had uricosuric properties. This led to the screening of a series of this type of compound and to the discovery that uricosuric action varied inversely with the pK. This in turn led to the testing of other drugs, some of which, notably G. 28315, have marked uricosuric action but little anti-inflammatory effect or none.

BOOK REVIEW

Roentgen Manifestations of Rheumatoid Arthritis. By Pekka Soila. 1958. Pp. 144, 63 figs, 10 tables. *Acta Rheumatologica Scandinavica*, Supplement I. Stockholm (Sweden), Turku (Finland).

The approach in this, the first supplement from *Acta rheumatologica*, is in the classic tradition of the monographs of *Acta radiologica*. More than one thousand patients, five areas radiographed, eleven radiological signs—this is the basis of a detailed description and exhaustive analysis.

About half the book is given over to an account of the radiological appearances in the hands, wrists, feet, ankles, and knees. Little is here that has not been said before, and this section remains a full exposition of descriptive radiology. It is unfortunate that the reproductions are not clear enough to recommend this work to a novice.

With this wealth of material, a statistical approach, which the reviewer takes on trust, becomes possible. Analysis of each radiographic sign in each joint, by sex, age group, and duration of the disease, is undertaken. The early signs are stressed, sex difference outlined, and a radiological staging for each joint suggested. An example of the information produced comes from the discussion of the frequency of appearance of alignment changes in the feet. A statistically significant rise is shown in both sexes 2½ years after the onset of the disease, and a second significant rise occurs after 5 years in women only. In the midst of this detail one is forced again and again to consider the selection of cases. The series was confined to the age group 20 to 49, the sex distribution was three women to two men, the diagnosis "was established by the generally accepted criteria", the joints were radiographed only "in the presence of clinical changes". The numbers are so large, however, that the conclusions are unlikely to be unacceptable, and the conclusions are presented with a backing of observation not approached in previous accounts.

IFOR WILLIAMS.

LIGUE EUROPÉENNE CONTRE LE RHUMATISME

Fourth Congress, Istanbul, 1959

A meeting of the Ligue Européenne contre le Rhumatisme will be held in Istanbul from September 28 to October 1, 1959. All those wishing to attend or to read papers should communicate as soon as possible with the Secretary of the Turkish Committee, 4th European Congress of Rheumatology, Tip Fakultefi, Fizik Tedavi, Klinigi, Cebeci, Ankara, Turkey.

In connexion with the Congress, arrangements are being made for those wishing to go by sea to leave Genoa on September 23 on the *S.S. Ankara* (6,000 tons, taking a total of 475 passengers), calling at Naples and Piraeus, and arriving at Istanbul on September 27. Delegates may live aboard throughout the congress and the *Ankara* will return to Naples *via* Izmir and the Greek Islands on October 6. Inclusive bookings at return party rates may be made through Thos. Cook and Sons, to include travel also to and from London. It will be necessary to leave London not later than 11 a.m. on September 22, arriving back at 8 p.m. on October 7.

SOCIETÀ ITALIANA DI REUMATOLOGIA

Fourth Acqui Prize, 1959

The closing date for entries has been extended to May 31, 1959. Competitors should enclose a brief resumé of their work in French or Italian. The panel of adjudicators will be announced after the last date of entry. Particulars may be had from the Azienda Autonoma di Cura di Acqui Terme, Piedmont, Italy.

NEW ZEALAND RHEUMATISM ASSOCIATION

Annual General Meeting, 1958

The eleventh annual general meeting was held at the Wellington Hospital, Wellington, on October 31 and November 1, 1958. The President, Dr. Basil Quin, was in the Chair, and twenty members were present. The following officers were elected for 1959-60:

President: Dr. A. Rowatt Brown.
Vice-President: Dr. B. S. Rose.
Hon. Sec. and Treasurer: Dr. F. H. Swan.*
Executive: Drs. Basil Quin and E. G. Sayers (*ex officio*), Drs. C. Gresson, J. M. Tweed, I. C. Isdale, T. C. Highton, M. Gilmour, Prof. H. Nisbet.

At the clinical meeting the following papers were given:

Childhood Deprivation as a Factor in the Epidemiology of Rheumatoid Arthritis, by Dr. B. S. Rose and Dr. I. C. Isdale (*Rotorua*): Deprivation during childhood, through parental death and other causes, was significantly more common in hospital patients with rheumatoid arthritis than in control subjects in the general population. The prevalence of such deprivation among rheumatoid subjects in the general population was not significantly greater than in controls.

Childhood deprivation, therefore, might help to determine the eventual need for medical care in the context of modern Western culture. Observations about the aetiological significance of environmental factors in rheumatoid arthritis, made only on those seeking such care, should be interpreted with caution.

Auto-Antibodies in Disseminated Lupus Erythematosus, by Dr. R. G. Wigley (*Palmerston North*): The evidence supporting the auto-immunization theory of the pathogenesis of disseminated lupus erythematosus was reviewed, and the value of routine tests for auto-antibody-like substances in the diagnosis of this disease was discussed.

Irritant Substance in the Synovial Fluid of Patients suffering from Rheumatoid Arthritis, by Dr. T. C. Highton (*Dunedin*): Synovial fluids from patients with rheumatoid arthritis were compared with fluids from joints affected by degenerative joint disease and osteochondritis dessicans. The tests were made with:

(1) Cell-free fluids.
(2) Cells derived from the fluids by centrifuging and resuspending in a minimal amount of fluid.

0·05 ml. of (1) or (2) was then injected intradermally into the abdominal wall of rabbits, and 10 minutes later 5·0 ml. 1 per cent. Congo red was injected intravenously. The resulting area of staining, measured at intervals thereafter, was assumed to be proportional to the amount of damage produced. By this criterion a significantly greater amount of damage was produced by cells and fluids derived from joints affected with rheumatoid arthritis.

Other differences indicating greater damage by cells and fluids of rheumatoid origin were also noted. The reactions were not abolished by previous injections of antihistamines.

Similar tests were carried out on rats, using Selye's "granuloma pouch" as a test object. The results also indicated the presence of a substance irritant to tissues derived from the mesenchyme in cells and fluids from rheumatoid joints.

Surgery in Some Rheumatic Diseases, by Mr. H. K. Christie (*Wanganui*): Cases were classified as rheumatoid proper and osteo-arthritic.

The new problems created by side-effects of corticosteroids were discussed. Splints, plasters, and manipulations were described.

The three criteria for surgical operations were based on anatomy, mechanics, and physiology, the last being too often forgotten.

The objects of surgery were prophylaxis, correction of deformity, restoration of movement, relief of pain, and treatment of complications. Individual joint surgery, especially in knee and foot, was described. The paper concluded with a counsel of forbearance and conservatism in surgery in rheumatic patients.

A Little-known Variant of the Rheumatic Syndrome, by Dr. R. D. Ballantyne (*Hastings*): Five cases of an apparently rare syndrome were described. It seemed to be a rheumatic condition characterized by constitutional disturbance and pain of centripetal distribution not conforming to descriptions of known rheumatic diseases.

Although a few cases caused anxiety the prognosis appeared good in most, and treatment with salicylates, ACTH, or cortisone had been effective.

Spinal Osteoporosis arising in the Course of Steroid Therapy, by Dr. Christopher Gresson (*Christchurch*): Ten cases of vertebral crush fracture were reported in rheumatoid arthritics receiving long-term steroid therapy. An incidence of 20 per cent. was observed where duration of therapy exceeded 5 years.

It was recommended that androgen-oestrogen therapy be given concurrently with long-term steroid therapy.

A Review of Cases of Ankylosing Spondylitis, by Dr. A. Rowatt Brown (*Auckland*): The patients with ankylosing spondylitis who had attended the Rheumatism

* Communications should in future be addressed to: The Hon. Sec., New Zealand Rheumatism Association, Dr. F. H. Swan, Department of Physical Medicine, Auckland Hospital, Auckland, New Zealand.

Clinic, and Physiotherapy and Radiotherapy Departments at Auckland Hospital in the period 1946 to 1958, had been reviewed. Almost all had received *x*-ray treatment at some stage, but many who had received radiotherapy had not attended the other departments. Of a total of 228 patients, 201 were male and 27 female. The average age at onset was 27 years, the youngest being 17.

Replies to a follow-up questionnaire were from 118 patients and three had died. 85 per cent. of those on the Rheumatism Clinic and Physiotherapy Department list and 79 per cent. of those on the Radiotherapy Department list were able to work.

No cases of leukaemia were found.

Review of Treatment of Rheumatoid Arthritis, by DR. E. J. CRONIN (*Auckland*).

Carpal Tunnel Syndrome, by MR. J. H. SAUNDERS (*Wellington*).

Observations on Vital Capacity in Rheumatoid Arthritis, by DR. I. C. ISDALE (*Rotorua*).

Experience with Rheumatic Fever in Northland, by DR. CLIVE GARLICK (*Whangarei*).

Cervical Spondylosis: A Review of 100 Cases, by DR. J. D. BERGIN (*Wellington*).

The following clinical demonstrations were arranged by Dr. J. MOORE TWEED (*Wellington*):

(1) A girl aged 14 with recurrent joint pains and fever following apparent rheumatic fever at age 8. Marked Raynaud's phenomenon had developed, and there had been transient patches of erythema on the cheek and neck. Full investigations had not made accurate diagnosis possible.

(2) A child aged 8 with juvenile rheumatoid arthritis from age 3 had been managed with emphasis on functional activity with good result. Reduction of growth was due to the disease.

(3) A woman aged 52 with Felty's syndrome or two unrelated conditions (rheumatoid arthritis and agranulocytosis of unknown origin). Long-standing mild polyarthritis, 260 polymorphs per c.mm., splenomegaly, marrow suggesting maturation arrest.

(4) A woman aged 34 with diffuse chondritis causing hoarseness, collapse of nasal septum, distorted pinnae, effusions in knee, tender metatarso-phalangeal joints, and widespread pain and stiffness.

(5) A man aged 75 with scleroderma.

(6) A man aged 30 with scleroderma and calcinosis.

(7) A woman aged 74 with calcinosis circumscripta of gradual onset and slow progression, with little pain and disability. Inconclusive attempt at increasing calcium elimination by use of disodium versenate. (Dr. J. D. MCCREANOR)

(8) A woman aged 49 with fever, polyarthritis, recurrent morbilliform rash, left heart failure, pericardial effusion, large soft tissue swellings in the supraclavicular fossae, and petechial eruption during recovery on steroids. (Dr. G. F. HALL)

(9) A woman aged 41 developed exfoliative dermatitis a week after eight weekly injections of 0·05 gm. Myocrysin. She recovered after 5 weeks and was discharged, but 2 weeks later (8 weeks after last gold injection) she developed thrombocytopenia and died from cerebral haemorrhage. (Dr. J. M. TWEED)

Ann. Rheum. Dis. (1958), **18**, 71.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi *of steroid therapy.*

Acute Rheumatism

Prevention of Rheumatic Fever Recurrences. BYWATERS, E. G. L., and THOMAS, G. T. (1958). *Brit. med. J.*, 2, 350. 14 refs.

During the years 1949 and 1950 at the Canadian Red Cross Memorial Hospital, Taplow, Bucks, 96 patients were diagnosed as having rheumatic fever, the criteria for diagnosis formulated by Duckett Jones (1944) as modified by the American Heart Association, being fulfilled in all cases. Four died in hospital and the remainder, who received no prophylactic chemotherapy, were followed up (with the exception of one who died and six who defaulted) for 5 years. During 1951 and 1952, 88 cases of rheumatic fever were diagnosed according to the same criteria, but (apart from two who died) during their stay in hospital and subsequently these patients received 1 g. daily of "sulphatriad" (a mixture of equal parts of sulphathiazole, sulphadiazine, and sulphamerazine); of the 86 survivors, 79 were followed up for 4 years and 71 for 5 years. Of the earlier group, eighteen suffered 24 episodes of fresh rheumatic activity during the follow-up period (14 one attack, two two attacks, and one three attacks of rheumatic fever, and one three attacks of chorea); in nine of these "recurrent" cases the patient was subsequently given prophylactic treatment and had no further attacks. Of the 1951-52 group, five had a further attack of rheumatic fever. Thus the mean incidence of recurrences per patient per year was 5·6 per cent. in the "unprotected" and 1·2 per cent. in the "protected" group. Toxic reactions to the drug were few. Two patients complained of lassitude and were found to have a low leucocyte count, but recovered when penicillin was substituted for sulphonamides, while one developed urticaria after 10 weeks' treatment.

Since 1952 all patients with rheumatic fever or chorea have been given prophylactic treatment with sulphatriad or benzylpenicillin (200,000 units twice daily) in hospital and after discharge. Although information as to any difference in the recurrence rate between the patients receiving the two drugs is not yet available, the authors' original favourable impression has been confirmed and toxic reactions have continued to be few and harmless, usually occurring within a few weeks of starting treatment and while the patient is still in hospital. The relative merits of the two forms of prophylaxis and the dosage and duration of administration are discussed briefly. *C. Bruce Perry.*

Prevention of Rheumatic Fever by Treatment of Streptococcal Infections. II. Factors Responsible for Failures. CATANZARO, F. J., RAMMELKAMP, C. H., and CHAMOVITZ, R. (1958). *New Engl. J. Med.*, **259**, 51. 12 refs.

The relationship between clinical, bacteriological, and immunological factors and the development of rheumatic fever was studied over a 5-year period at the Francis E. Warren Air Force Base, Wyoming, in 5,198 patients with infection due to Group-A streptococci. All the patients were treated with sulphadiazine or an antibiotic.

Rheumatic fever developed in 76 of the patients, but 27 were excluded from the investigation either because the latent interval was too long for the disease to be attributable to the same streptococcal infection, or because signs and symptoms of rheumatic fever developed during the first 72 hours of the streptococcal infection, making assessment of the efficacy of specific treatment uncertain. In the remaining 49 patients with latent periods of 4 to 45 days, the rheumatic fever was considered to be related to the preceding streptococcal infection.

It was found that a previous attack of rheumatic fever or recent contact with streptococcal infection slightly increased susceptibility to rheumatic fever. Further, the continued presence of the infecting organism during the convalescent phase after treatment was a highly significant factor in the subsequent development of rheumatic fever, the organism being present in 62 of the 76 patients with rheumatic fever but in only 20 per cent. of the remainder of the population studied.

The authors conclude that the most important factor in causation of rheumatic fever following streptococcal infection is failure to eradicate the organism by treatment.

They also emphasize the need for effective antibiotic therapy (penicillin parenterally rather than by mouth) and for continuous prophylaxis in patients who have had rheumatic fever previously. They add that sulphonamides should never be given in treatment since they do not eliminate the *Streptococcus*.

Gerald Sandler.

Differential Diagnosis of Rheumatic Fever. HALLIDIE-SMITH, K. A., and BYWATERS, E. G. L. (1958). *Arch. Dis. Childh.*, **33**, 350. 23 refs.

The differential diagnosis of rheumatic fever is discussed on the basis of 9 years' experience (1947 to 1956) at the Centre for Juvenile Rheumatism, Canadian Red Cross Memorial Hospital, Taplow, Bucks. Of 2,214 patients admitted to the unit over this period, 959 were discharged with a diagnosis of rheumatic fever, the criteria for diagnosis being those of Duckett Jones (*J. Amer. med. Ass.*, 1944, **126**, 481), with modifications. A group composed of one-sixth of these 959 patients was selected, and it was found that in twelve of the 160 patients rheumatic fever was not diagnosed initially, the erroneous diagnoses including pneumonia, meningitis, rubella, dysentery, subacute bacterial endocarditis, appendicitis, suppurative arthritis of the hip, Still's disease, and fallen arches. A group of 196 patients was admitted to the hospital with a diagnosis of rheumatic fever, but this was not substantiated. The final diagnoses in this group were:

Functional disorders (eight, including three with physiological tachycardia);

Traumatic and postural disorders (eleven);

Infections (91, including 55 with respiratory-tract infections, 16 with specific fevers, and ten with bone or joint infection);

Connective-tissue disorders (42, including 24 with Still's disease or rheumatoid arthritis and eight with Schönlein-Henoch purpura);

Rheumatic and congenital heart disease (nine, of whom seven had established rheumatic heart disease, although there was no evidence of active rheumatism);

Blood dyscrasia (two);

Others, including arthritis of unexplained origin, arthralgia, and limb pain (33).

The clinical features pointing to a diagnosis of rheumatic fever are described, and the common erroneous interpretations of the history and of the presence of fever, tachycardia, and systolic murmurs are discussed. The authors emphasize the importance of recognizing even mild cases of rheumatic fever now that the efficacy of sulphonamide or penicillin in the prevention of the disease has been established. They consider that fuller investigation at an early stage, particularly estimation of the erythrocyte sedimentation rate and a search for streptococcal infection, would be helpful in the less obvious cases.

C. E. Quinn.

Blood Culture Studies in Rheumatic Fever Patients. SCHEFF, G. J., MARIENFELD, C. J., and HACKETT, E. (1958). *J. infect. Dis.*, **103**, 45. 20 refs.

The authors have returned to the attack on the problem of isloating and identifying a possible causative agent in rheumatic fever, and in this communication from the University of Illinois, Chicago, they present the results of the culture of 509 blood samples taken from 285 children aged 5 to 15 years, of whom 185 were in various stages of rheumatic fever and the remaining 100 served as controls. A full description is given of the precautions taken in obtaining the blood by venepuncture and of the culture medium, a brain-heart infusion containing 0·1 per cent. agar, using 5 ml. blood to 45 ml. freshly prepared medium. The flasks were cultured for periods of up to 35 days since growth at first is very slow, opened on the appearance of turbidity or discoloration, and an inoculum usually passaged to a further broth culture before spreading on solid 5 per cent. blood agar. About five colonies were selected for further identification, which was based on morphological, biochemical, and physical characteristics as well as serological investigation using anti-A and anti-D antisera in a micro-precipitin test.

Organisms, which were found to be almost exclusively enterococci, were first isolated after 15 days in 43 out of fifty cases, and all except one were isolated within 30 days' incubation. Pure cultures were grown in each instance and all had the same cultural characteristics. Of 79 cultures from 36 patients in the acute stages of rheumatic fever but not receiving antibiotics or sulphonamides 41 (52 per cent.) were positive (equivalent to 66 per cent. of the patients), while of those from eighty patients who were receiving antibiotics or sulphonamides only nine (11 per cent.) were positive (24 per cent. of the patients). Somewhat similar figures were found in convalescent patients and those with inactive disease, with a slightly higher proportion of isolations in those patients who were not receiving antibacterial treatment. Of the cultures from the 100 control cases 14 per cent. of those from febrile subjects and only 4 per cent. of those from non-febrile subjects (mostly one culture per patient) were positive.

Morphologically the isolated organisms appeared predominantly as Gram-positive diplococci showing some variation in size. In tests for haemolysis on horse-blood agar plates more colonies manifested β-haemolysis than γ-haemolysis, whereas on the human-blood plates this ratio was reversed; distinct α-haemolysis was not observed. The biochemical characteristics of the organisms resembled for the most part those of enterococci. Serological tests showed that 34 out of 38 reacted with Group D serum; seven were grouped as A. It would be reasonable to suggest that these enterococci enter the blood stream from the gastro-intestinal tract, but work in progress, using the tetrazolium reduction test for closer identification, has shown that the organisms isolated in this study differed markedly from bacteria of known faecal origin. The authors conclude: "Although no claim is made regarding relationship to rheumatic fever, it is felt that the enterococci invading the blood

stream are not incidental but may play a contributory role in the disease picture."

E. G. L. Bywaters.

"Rheumatic" Pneumonia with Pulmonary Hyaline Membrane. (Über die sog. rheumatische Pneumonie mit pulmonalen hyalinen Membranen.) LAPP, H., and MALECH, G. (1958). *Frankfurt. Z. Path.*, **69**, 194. 3 figs., 25 refs.

With reference to three cases examined *post mortem* at the Pathological Institute of the Justus Liebig University, Giessen, the author discusses the morbid anatomy of the pneumonic condition occasionally associated with rheumatic carditis. Macroscopically, the lungs show ill-defined areas of consolidation, not confined to any one lobe; the consistency of these areas is less firm than in the hepatization of lobar pneumonia and their colour depends on the amount of cardiac back-pressure which has been present. Histologically, there is a non-suppurative, partly haemorrhagic pneumonia, with hyaline membranes lining the alveoli and terminal bronchioles. The thickness of the membranes varies from a few microns upwards; they are sharply demarcated from the alveolar wall, and occasionally a connection between the membranes in adjacent alveoli through the alveolar pores may be seen. Irregular coarse layering of the hyaline material can sometimes be seen, and it may be acellular or contain round cells of varying size. Some alveoli contain spherical hyaline masses (Masson bodies) enclosing alveolar epithelial cells and showing signs of organization by ingrowing fibroblasts. The hyaline material can be distinguished from oedema fluid and from fibrin by its staining reactions; it gives a positive periodic-acid-Schiff reaction. No neutral fat is demonstrable. There is also proliferation of the pericapillary endothelium to form large cells, usually mononuclear but occasionally multinuclear, with a basophil cytoplasm. These cells may be found in the alveolar lumen and in the Masson bodies.

The author considers that there is a fundamental difference between the pulmonary hyaline membranes found in uraemia, plague, and poisoning with phosgene and other substances in man and in experimental oxygen and carbon dioxide poisoning in animals, in which the hyaline material is derived from necrotic alveolar cells, and those found in interstitial plasma-cell pneumonia of the newborn, poliomyelitis, pneumonia of premature infants, and rheumatic pneumonia, in which it lies on a healthy alveolar wall. The author suggests that although the latter group contains conditions of widely differing aetiology the hyaline material in all of them is derived from the blood. In the rheumatic process there is a disturbance of the ground substance of connective tissue which is reflected in an increase in the serum glucoprotein and globulin content. This dysproteinaemia may account for the unusual appearance of the inflammatory exudate in rheumatic pneumonia, and a similar mechanism may operate in the other conditions mentioned.

F. Hillman.

Changes in the Laboratory Findings during the Course of Rheumatic Carditis treated with Hormones. (Variations biologiques au cours des cardiopathies rhumatismales sous hormonothérapie.) SARROUY, C., SENDRA, L., CABANNES, R., GILLOT, F., RAFFI, A., and RAOUX, J. P. (1958). *Arch. franç. Pédiat.*, **15**, 736. 36 refs.

At the Children's Medical Clinic of the Faculty of Medicine, Algiers, a number of biochemical estimations were serially performed on 32 patients with rheumatic carditis, of whom 24 had active disease, three had chronic valvular disease with smouldering activity, and five had had rheumatic carditis in the past. In order to establish normal baseline values the same investigations were also performed on twenty healthy subjects, while ten further patients suffering from a variety of diseases were also investigated in order to test the specificity of the procedures employed; these were determination of the erythrocyte sedimentation rate (E.S.R. (Wintrobe)), and of the serum fibrinogen, hexosamine, polysaccharide, and mucopolysaccharide levels, a test for the presence of C-reactive protein, and estimation of the antistreptolysin-O (A.S.O.) titre; the serum proteins and serum sugars were investigated by electrophoresis. The overall object of the study was to discover whether it was possible to establish a battery of tests which would be specific for the diagnosis of doubtful cases, and which could be used to assess the gravity of the illness at onset, to follow the course of the disease and guide management during treatment, and finally to help in determining the prognosis. The patients with rheumatic carditis were all treated with prednisolone, starting with 30 mg. daily later reduced to 10 mg. daily, and terminating with three injections of 75 mg. ACTH on consecutive days. The minimum duration of hormone treatment was 45 days.

Though the combined test results were suggestive of the diagnosis of rheumatic fever before treatment was begun, none was found to be specific, the results being virtually the same as those found in a variety of unrelated disorders, for example, leukaemia. In patients with acute rheumatic fever, a normal E.S.R. was found in one case and a normal serum fibrinogen level in another; the total serum polysaccharide, mucopolysaccharide, and C-reactive protein levels were elevated in all cases, and the serum hexosamine level in all but four, while the A.S.O. titre was below the normal value of 200 in three cases. The electrophoretic pattern of the serum proteins was always abnormal, the albumin fraction being decreased and the α_2-globulin and γ-globulin fractions increased. The serum sugar pattern was often normal. The degrees of departure from normal of the various tests usually correlated with each other and with the clinical severity of the case, but not with the ultimate prognosis.

During hormone treatment the E.S.R. fell rapidly in favourable cases and remained normal, provided the dose was sufficient, but in a few in which the clinical outcome was unfavourable the E.S.R. remained high. The variations in the serum fibrinogen level were inconsistent and unreliable. The serum total polysaccharide, hexosamine, and C-reactive protein levels tended to

follow the E.S.R., but the A.S.O. titre was not influenced by treatment. The changes in the serum protein fractions tend to revert towards normal. It is pointed out that after the conclusion of treatment the rebound phenomenon may occur, during which the various changes described above tend to follow the pattern set by the E.S.R. It is finally concluded that none of these tests except the E.S.R. is essential for following the progress of a case of acute rheumatic fever.

[The number of estimations, the interval between them, and the actual values obtained are not given in the paper.]

John Lorber.

Serum Oxaloacetic Transaminase Activity in Acute Rheumatic Fever. Values in Cases with and without Salicylate Therapy. MASSIE, R. W., and STAHLMAN, M. (1958). *A.M.A. J. Dis. Child.*, **95**, 469. 7 figs, 8 refs.

In a study at Vanderbilt University, Nashville, Tennessee, the authors determined the glutamic oxalacetic transaminase (G.O.T.) activity in the serum of eighteen cases of rheumatic fever and endeavoured to correlate it with other indices of acute-phase activity and with medication. These eighteen cases, sixteen of them in children between 6 and 14 years of age, were followed up for 3 to 15 months. G.O.T. activity was determined according to the method of Karmen, Wroblewski, and La Due (*J. clin. Invest.*, 1955, **34**, 126), values above 40 units being taken as abnormal. A series of seven individual charts are given showing serial estimations of erythrocyte sedimentation rate, serum G.O.T., C-reactive protein, antistreptolysin-O titre, salicylate level, salicylate medication, and "clinical activity" (assessed independently of the above indices). Although there was a tendency for the serum G.O.T. level to be raised in the acute phase of rheumatic fever (thirteen out of eighteen cases), as also occurs in other instances of tissue damage, the changes in level were inconstant. Rheumatic carditis was not always accompanied by a rise in the G.O.T. level, although raised values were seen only in patients with rheumatic carditis. There was a slight parallelism between other acute-phase indices in some patients, and in others there was a striking rise in the level coincident with the administration of salicylate.

Control studies were devised to elucidate this last phenomenon, but no effect was found in studies *in vitro* using salicylate levels up to 40 mg. per 100 ml., nor were any changes found after large doses of salicylate in a normal subject or a patient with severe congestive failure and hepatomegaly. There was no change in patients with a raised serum G.O.T. level due to liver disease given salicylate treatment for 7 days, nor in a patient recovering from acute salicylate intoxication. Various hypotheses were examined to account for these rises in serum G.O.T. level during salicylate therapy, but none of them seemed to the authors entirely satisfactory. A single determination of G.O.T. activity was of little value in diagnosis or in following the course of the disease.

E. G. L. Bywaters.

Pathology of Rheumatic Fever treated with Corticosteroids. (Patología de la fiebre reumática tratada con corticosteroides.) BARROSO-MOGUEL, R. (1958). *Gac. méd. Méx.*, **88**, 407. 10 figs, 37 refs.

In this paper from the National Institute of Cardiology Mexico, the author reviews the pathological findings in thirty fatal cases of clinically typical rheumatic fever which had been treated mainly by corticosteroid therapy. The macroscopic findings, which did not appear to have been influenced by the treatment, included valvular vegetations in 24 cases, fibrinous pericarditis in thirteen, pneumonitis in eleven (severe in seven), and encephalitis in one.

The histological appearances on the other hand were considerably influenced by the treatment, and the following features seemed to be associated with high doses and long courses of corticosteroids. The valvular vegetations showed markedly cell-free accumulations of unorganized Schiff-positive material with minimal tissue reaction in the underlying valve despite clinical evidence of prolonged valvular involvement. Fibrinoid necrosis was especially severe and widespread, with little tendency to organize and reabsorb, and it frequently involved also both the cardiac and visceral blood vessels. Aschoff bodies were seen in thirteen cases, but appeared to be typical only in the three cases which had received the least treatment, the lesions in the remainder showing a fibroblastic transformation. Large cells with intensely blue-staining cytoplasm were sometimes seen along with the Aschoff bodies; in some cases the cytoplasmic staining obscured the cell nucleus sufficiently to produce an appearance resembling the haematoxylin bodies of disseminated lupus erythematosus. The lungs showed unusually severe fibrinoid infiltration around the alveolar blood vessels. The intra-alveolar exudate was poorly organized and eventually formed numerous Masson bodies, while the proliferation of the alveolar lining cells and parenchymal fibrosis produced in some cases a histological picture indistinguishable from that of the Hamman-Rich syndrome. Lymphocytic infiltration of the myocardium occurred in 28 cases, but its severity was not related to the dose of corticosteroids; nevertheless, the infiltration could be very extensive even when large doses had been given. The pericardium showed unusually severe fibroblastic reaction and there was unusually severe fibrinoid necrosis in the underlying connective tissue.

In her conclusions the author suggests that corticosteroids may (1) increase fibrinoid necrosis in rheumatic fever, and (2) transform Aschoff cells into active fibroblasts.

Allan St. J. Dixon.

Relation between C-reactive Protein and Erythrocyte Sedimentation Rate in Rheumatic Fever. ROZANSKY, R., and DAVIS, E. (1958). *Amer. J. clin. Path.*, **29**, 331. 1 fig., 11 refs.

The authors report from the Rothschild-Hadassah University Hospital, Jerusalem, a study of the C-reactive protein (C.R.P.) content of the serum and the erythrocyte sedimentation rate (E.S.R., Westergren) in 448 patients (adults and children) with rheumatic fever or rheumatic

heart disease, 700 specimens of blood being examined. There was a well-marked correlation between the results of the two estimations. The discrepancies, however, were informative. C.R.P. was present in 15 per cent. of the specimens showing a normal E.S.R. In specimens of blood from nine patients with active rheumatic fever and congestive heart failure the reaction to the C.R.P. test was strongly positive and the E.S.R. was normal. The response to the C.R.P. test was negative in 40 per cent. of specimens showing an E.S.R. between 21 and 50 mm. per hour, probably because C.R.P. usually disappears from the serum before the E.S.R. reaches normal levels.

In five out of 22 pregnant women suspected of having rheumatic activity the result of the C.R.P. test was negative although the E.S.R. was above 50 mm. in one hour. The authors consider that in such cases rheumatic activity could probably be excluded, since a number of workers have found that during normal pregnancy the E.S.R. is usually raised but the response to the C.R.P. test is positive in from 17 to 32 per cent. of cases. *E. G. L. Bywaters.*

Serum Mucoprotein Content as a Diagnostic Index and Measure of Activity in Rheumatic Fever in Children. (Le mucoproteine quale indice diagnostico e di attività della malattia reumatica in pediatria.) QUARTI, M., TARANTINO, M., and VASSENA, E. (1958). *Osped. maggiore*, **46**, 95. 23 refs.

This paper from the University of Milan reports the results of the estimation of serum mucoprotein levels in 98 patients with rheumatic fever. The technique of estimation is given in detail. Of these 59 male and 39 female patients, ranging in age from 4 to 13 years, 74 were in-patients at the Ospedale Maggiore of Milan, and in these the estimations were performed before treatment with prednisone or phenylbutazone and repeated after recovery. The other 24 children were apparently well but had a history of previous rheumatic fever.

In many cases the serum mucoprotein level was raised during the acute phase of the disease, but tended to become normal later. Very high levels were often associated with a markedly raised erythrocyte sedimentation rate. It is concluded that an increase in the serum mucoprotein level is of diagnostic value, but is not an absolute expression of the activity of rheumatic fever. *David Friedberg.*

Experiences with the Treatment of Acute Rheumatic Fever with Prednisone. (Naše zkušenosti s léčbou akutního revmatismu prednisonem.) VONDRÁKOVÁ, I., VINTERA, J., and KRČÍLKOVÁ, M. (1958). *Čsl. Pediat.*, **13**, 704. 6 refs.

Clinical and Statistical Study of the Incidence of Rheumatic Fever and Cardiopathy in Children attending Primary Schools in Bari. (Indagine clinico-statistica sulla frequenza delle cardiopatie e della malattia reumatica tra gli alunni di scuole primarie di Bari.) COLONNA, L., RICCIARDI, G., CANDELA, V., and GIORDANO, S. (1958). *Reumatismo* **10**, 178. 1 fig., 15 refs.

Rheumatic Fever. A Follow-up Report of the St. Louis Secondary Prevention Program. SMITH, J. E., and WAITT, P. (1958). *Missouri Med.*, **55**, 1095.

Study of the Manifestations of Rheumatic Fever following Cessation of Therapy. FISCHEL, E. E., FRANK, C. W., and BELLOWS, M. T. (1958). *Circulation*, **18**, 367. 6 refs.

Clinical Picture of Rheumatic Fever. II. Therapeutic Considerations. (Il quadro clinico della febbre reumatica. II. Considerazioni terapeutiche.) MASSELL, B. F., FYLER, D. C., ROY, S. B., and PELARGONIO, S. (1958). *Progr. med. (Napoli)*, **14**, 321. 1 fig., 1 ref.

Streptolysin Reactions in Children suffering from Rheumatic Fever. (Odczyny streptolizynowe u dzieci z chorobą reumatyczną.) CHMIELOWA, M. (1958). *Pediat. pol.*, **22**, 797. 6 refs.

Chronic Articular Rheumatism (Rheumatoid Arthritis)

Triamcinolone in Treatment of Rheumatoid Arthritis. HARTUNG, E. F. (1958). *J. Amer. med. Ass.*, **167**, 973. 9 refs.

Triamcinolone, a new cortisone analogue, was tried in the treatment of 67 patients with rheumatoid arthritis, 23 of whom were given the drug for over 6 months. The suppressive effect on the arthritis of an average dose of 10 mg. a day was satisfactory but was slower than that of prednisone or prednisolone. In the author's view some side-effects of treatment, such as hypertension, symptoms of peptic ulceration, euphoria, and oedema, were less severe with triamcinolone than with other steroids, but weight loss, night cramps, and masculinizing effects were more marked. *Oswald Savage.*

Triamcinolone. HART, F. D., GOLDING, J. R., and BURLEY, D. (1958). *Lancet*, **2**, 495. 2 figs, 9 refs.

Triamcinolone (16-α-hydroxy:$\triangle^1$:9-α-fluorohydrocortisone) is claimed to have less sodium retaining action, to cause fewer side-effects (particularly peptic ulceration), and to have an equally potent antirheumatic effect as compared with prednisone and prednisolone, when given in four-fifths of their dose. The authors therefore carried out a short-term trial at the Westminster Hospital, London, to assess the last two of these claims, 24 patients with rheumatoid arthritis and one with psoriatic arthropathy being given 5-mg. tablets of prednisolone until improvement was maintained at a constant level, and treatment then changed to the same number of 4-mg. tablets of triamcinolone, that is, the dosage was reduced to four-fifths; after a period ranging from 5 to 70 days the patient was again given prednisolone. A positive result was recorded only when improvement occurred on changing to triamcinolone and deterioration on changing from it.

None of the patients showed any significant change in erythrocyte sedimentation rate or finger tenderness, while five reported significant subjective improvement while taking triamcinolone. Of the seven patients with gastro-duodenal symptoms, three were improved, one was unchanged, and three were worse after changing to triamcinolone; in two patients large abdominal striae appeared while taking triamcinolone. Improvement of the skin condition occurred in the one psoriatic patient. In three patients with systemic lupus erythematosus and two with ulcerative colitis triamcinolone produced little change as compared with prednisolone.

The authors conclude from this admittedly short trial that triamcinolone is an effective steroid, but has few advantages over prednisolone, apart from its lack of salt and water retaining action. Mild side-effects may be commoner, but the incidence of serious side-effects can only be determined by more extensive trials (although some were seen in this series). A slight preference is expressed for triamcinolone. *B. E. W. Mace.*

16α-Methyl Corticosteroids. A New Series of Anti-inflammatory Compounds; Clinical Appraisal of Their Antirheumatic Potencies. BOLAND, E. W. (1958). *Calif. Med.*, **88**, 417. 1 fig., 14 refs.

Over the past few years many attempts have been made to produce synthetic steroid compounds which retain their anti-inflammatory action but are free from the properties inducing deleterious physiological effects. Recently, a family of four hydrocortisone analogues with a methyl group at the 16α carbon position of the steroid nucleus have been synthesized, and on biological testing were found to possess markedly enhanced anti-inflammatory action unassociated with disturbance of electrolyte metabolism.

These four compounds, 16α-methyl-9α-fluoroprednisolone (MK-125), 16α-methyl-9α-fluorohydrocortisone (MK-126), 16α-methylprednisolone (MK-110), 16α-methylhydrocortisone (MK-117), were tried in the treatment of patients suffering from rheumatoid arthritis, and preliminary observations are reported in this paper from St. Vincent's Hospital, Los Angeles. The selection of patients was limited to those whose maintenance dose of prednisolone was well-established and stable but who had sufficient residual evidence of active joint inflammation to permit measurement of any changes. Treatment was given with first one drug and then another, and the dosage of each drug required to maintain equivalent clinical improvement, as judged subjectively and objectively, was determined. At least two cross comparisons were made in every case. The approximate differences between the compounds were: MK-125 was seven times and MK-126 three times more potent than prednisolone; the potency of MK-110 was only one-third greater than that of prednisolone; and the potency of MK-117 was only two-thirds that of prednisolone. None of these steroids caused signs of salt and water retention. The author states that the findings are in accord with the results of experiments in animals.

These preliminary observations indicate that MK-125 is the most effective anti-rheumatic agent so far produced, satisfactory control of the disease being achieved with a daily dosage of 0·6 to 2·8 mg. for periods up to 4 months. The author points out, however, that further prolonged observation is required before its value and potential hazards can be assessed.

It is concluded that the substitution of a methyl radical at the 16α position intensifies the anti-rheumatic action of certain 11-hydroxycorticosteroids.

B. M. Ansell.

Intra-Articular Therapy in Rheumatoid Arthritis. Comparison of Hydrocortisone Tertiary Butyl Acetate and Hydrocortisone Acetate. CHANDLER, G. N., WRIGHT, V., and HARTFALL, S. J. (1958). *Lancet*, **2**, 659. 1 fig., 5 refs.

In the treatment of 24 patients with rheumatoid arthritis principally involving the knee-joints (37 joints) at the General Infirmary at Leeds the authors have compared the results of intra-articular injections of hydrocortisone acetate and hydrocortisone tertiary butyl acetate (T.B.A.); the latter is a less soluble preparation which was introduced for intra-articular therapy in the hope of obtaining a more prolonged action. By the use of a double-blind, cross-over technique neither the patient nor the assessor knew which drug was being tried; all patients received both drugs and a placebo (the suspending vehicle) at different times so that each patient served as his own control. The dosage of both drugs was 25 mg. in 1 ml. vehicle, the placebo being 1 ml. vehicle. The injections were given in three courses of four fortnightly injections with 8 weeks' rest between courses.

The results were assessed every 2 weeks by the same observer throughout the trial, the final assessment being made by comparing the effects on pain, tenderness, walking time, range of movement, limitation of extension, erythrocyte sedimentation rate, and a subjective assessment. Both drugs produced significantly better results than the placebo. Although improvement appeared generally greater and more sustained with hydrocortisone T.B.A. than with hydrocortisone acetate the difference was not statistically significant. *William Hughes.*

Deleterious Effect of Intra-Articular Hydrocortisone. CHANDLER, G. N., and WRIGHT, V. (1958). *Lancet*, **2**, 661. 3 figs, 3 refs.

After the trial described above (see previous Abstract) the authors were disturbed to find that, despite the generally good clinical response, in many of the patients treated by intra-articular injections of steroids, radiological deterioration of the knee-joint had occurred. Thus, in eighteen subjects who completed the trial, radiographs of the knees taken before and after treatment revealed that thirteen out of 25 affected joints showed deterioration, in two cases severe. The *x*-ray findings were graded as to degree of osteoporosis, loss of joint space, and erosions before and after treatment.

The data were analysed to ascertain if any correlation

existed between radiological deterioration and clinical response. At the sixth week it was noted that the improvement in walking time after the injections was greater in those with radiological deterioration, the difference being statistically significant; this was the only significant difference noted. The authors regard the improvement in walking time as the attainment of a performance which is really beyond the capacity of the joint. They have observed elsewhere the development of a virtual Charcot's arthropathy in a rheumatoid arthritic patient who was treated for over 18 months by intra-articular hydrocortisone. They suggest that the intra-articularly injected steroid interferes with a locally protective mechanism and thus allows a greater range of movement, but in turn causes the radiological deterioration observed. *William Hughes.*

Increasing the Effectiveness of Gold Therapy in Rheumatoid Arthritis. SMITH, R. T., PEAK, W. P., KRON, K. M., HERMANN, I. F., DELTORO, R. A., and GOLDMAN, M. (1958). *J. Amer. med. Ass.*, **167**, 1197. 2 figs, 18 refs.

As part of a study at the Benjamin Franklin Clinic, Philadelphia, of the variable response to gold therapy in rheumatoid arthritis, the urinary secretion of gold was assayed on 138 occasions in a series of patients who had been given intramuscular injections of aurothioglucose and gold sodium thiomalate in a total dosage of 820 to 1,070 mg. in 24 weeks. Among patients who experienced a remission of arthritis approximately one-seventh of the dose of gold salt was excreted during the first week of administration, but among patients who showed intolerance the amount excreted was less than one-seventh of the dose. There was an approximate correlation between the total amount of gold salt administered, the excretion rate, and the onset of toxicity. Toxic reactions included pruritis, dermatitis, stomatitis, leucopenia, and disturbances of renal function. In one patient dermatitis developed after a total dose of 70 mg. aurothioglucose had been given, while in another the skin reaction did not appear until 820 mg. had been administered. In cases of hyper-retention of gold a total dose of 300 to 500 mg. had been administered before the onset of toxic reactions.

For the management of toxic reactions the authors advocate the omission of gold therapy and administration of prednisolone or prednisone in a daily dosage of 10 to 20 mg. If a rash occurs a steroid lotion may be applied locally. Dimercaprol is required only occasionally. From two-thirds to three-quarters of the previously planned dose of the gold salt should be instituted as maintenance therapy 2 to 3 weeks after the reaction has subsided and the steroid has been withdrawn. Before each injection an examination should be carried out for signs of irritation, rash, or soreness of the mouth, and the blood and urine should be examined. Every 4 weeks the laboratory tests should include a complete blood count and determination of the erythrocyte sedimentation rate.

A comparative study of the effects of gold therapy in two groups of patients showed that an "individualized" regimen was more effective than a standard regimen and induced a remission in 82 per cent. of cases. With adequate therapy a remission can be expected in 12 to 18 weeks, and is likely to persist with maintenance therapy for an average period of 8 months. *A. Garland.*

Gold in the Treatment of Rheumatoid Arthritis. LOCKIE, L. M., NORCROSS, B. M., and RIORDAN, D. J. (1958). *J. Amer. med. Ass.*, **167**, 1204. 7 refs.

Since 1940 at the General Hospital, Buffalo, N.Y., gold salts have been given to all patients with reversible rheumatoid arthritis who were otherwise in good health. The majority of the 369 patients received gold sodium thiomalate, but a few were given aurothioglucose. The gold salt was administered intramuscularly at weekly intervals, beginning with a dose of 10 mg., then 20 mg., and then 40 mg. weekly until a total of 500 mg. had been given. Thereafter the dosage was determined on the basis of the clinical status of the patient. The injection was given into the deltoid muscle, a 24-gauge ¾-inch (19·1-mm.) needle being used. There were no local inflammatory reactions with this technique.

Compared with a group of 566 controls the patients given gold salts had "a 20 per cent. better chance of complete recovery or major improvement". Favourable results were obtained in a relatively large number of patients suffering from moderate or severe rheumatoid arthritis, and the authors suggest this good response was due to close observation and treatment extending over a period of many months or years. A total dose of more than 300 mg. of the gold preparation was required in order favourably to influence the course of the disease. Severe side-effects were few, since care was taken to observe "the warning appearance of glossitis and dermatitis". The reactions were controlled by omitting gold treatment and administering antihistaminics, steroids, and dimercaprol when necessary. It is emphasized that although evidence of sensitivity to gold salts may appear at any time, the treatment can be continued for years without precipitating a reaction, provided there is careful and constant observation of the patient for signs of such sensitivity. In 50 per cent. of patients with mild reactions treatment can be continued although the dosage may have to be reduced.
A. Garland.

Treatment of Rheumatoid Arthritis with Chloroquine. (Die Resochinbehandlung der primär chronischen Polyarthritis.) BRAUNSTEINER, H., EGGHART, F., PÄRTAN, J., and WIEDERMANN, G. (1958). *Wien. Z. inn. Med.*, **39**, 248. 36 refs.

The authors report briefly the results obtained with chloroquine in the treatment of 103 cases of rheumatoid arthritis observed over a period of 2 to 6 months at the Second Medical University Clinic, Vienna. The drug was initially administered in a daily dose of 0·5 g., but in the majority of cases this was reduced after 2 to 3 weeks

to 0·25 g. daily in view of the frequent occurrence of side-effects, such as giddiness, followed by abdominal pain and vomiting, disturbance of accommodation, and insomnia. These occurred in 66 cases (65 per cent.) and were so severe in seven that the treatment had to be discontinued.

Some improvement was noted in 68 per cent. of cases, this effect usually appearing between the fourth and sixth weeks of treatment. One-third of these patients improved to such an extent that additional medication was only rarely necessary; the other two-thirds had to continue with their previous medication of glucocorticoids and analgesics, but in reduced doses. There were no cases of complete remission.

H. F. Reichenfeld.

Long-term Treatment of Rheumatoid Arthritis with Mepacrine and Chloroquine. (Langtidsbehandling af rheumatoid arthritis med mepacrin og chloroquine.) ERLENDSSON, F. (1958). *Ugeskr. Læg.*, **120**, 793. 18 refs.

The author reports the results obtained with mepacrine and chloroquine in the long-term treatment of fourteen patients (eleven women) with rheumatoid arthritis. All but four of the patients were over 50 years of age, and in six of them the onset of the illness had taken place at least 20 years previously. Except for one patient, all had disease graded as Stage II, III, or IV. The minimum daily dose of mepacrine was 100 mg., and that of chloroquine diphosphate 250 mg.

In seven patients who were followed up for 1½ to 3 years, the severity of the condition lessened by one or two Grades, while two others discontinued active treatment in view of their continued well-being. Toxic reactions made withdrawal of the drug necessary in five patients, four of these developing cardiac pain and one a rash. In three cases chloroquine was substituted for mepacrine without a break in therapy. Although no conclusions are reached regarding the type of case most suitable for this therapy, the author is convinced of the value of chloroquine in the treatment of rheumatoid arthritis. It is of interest that two patients who had failed to respond to cortisone showed marked improvement with the antimalarial drugs. Several detailed case histories are presented.

H. F. Reichenfeld.

Treatment with Chloroquine of Twenty Patients with Active Rheumatoid Arthritis. (Chloroquinebehandling of 20 patienter med aktiv rheumatoid arthritis.) ERLENDSSON, F. (1958). *Ugeskr. Læg.*, **120**, 800. 11 refs.

The treatment with chloroquine of sixteen female and four male patients suffering from active rheumatoid arthritis is described. Their ages ranged from 24 to 71 years and, with the exception of a 57-year-old woman in Stage IV, the disease was in Stages I, II, or III. Previous methods of treatment had included gold therapy in five cases and corticosteroid therapy in eight. Chloroquine therapy was started with a daily dose of from 500 to 750 mg. of the diphosphate, this being reduced to 250 to 500 mg. daily when either the onset of side-effects made it necessary or a good therapeutic response had been obtained.

After a period of treatment which in most cases lasted from 2 to 6 weeks, five patients had a complete remission, ten showed major and three minor improvement, and two were not improved. In ten cases the treatment was continued for further periods ranging from 80 to 700 days, and by this time the disease in six patients had regressed to Grade I and in the remaining four to Grade II. Similar assessment in another six cases, which responded to the initial course of treatment but in which chloroquine therapy had been discontinued, showed improvement to Grade I in four cases and to Grade II in two.

H. F. Reichenfeld.

Treatment of Rheumatoid Arthritis with Primaquine and Chloroquine. (Behandling af rheumatoid arthritis med primaquine-chloroquine.) ERLENDSSON, F. (1958). *Ugeskr. Læg.*, **120**, 804. 23 refs.

Detailed case histories are presented of six patients with active rheumatoid arthritis who were treated with an intensive course of antimalarial drugs at the Antssygehus, Aarhus, Denmark. This consisted in the administration of chloroquine diphosphate, 500 mg. three times daily and primaquine phosphate 7·5 mg. of the base, twice daily. Side-effects, in the form of diarrhoea, giddiness, sweating, and nausea, were so severe that treatment of one patient was stopped after 5 days, while the five others continued on a much reduced dosage for further periods of 11 to 60 days. On cessation of treatment, two of these cases showed improvement to Grade III and three to Grade II.

H. F. Reichenfeld.

***X*-Ray Manifestations of Peptic Ulceration during Corticosteroid Therapy of Rheumatoid Arthritis.** HILBISH, T. F., and BLACK, R. L. (1958). *A.M.A. Arch. intern. Med.*, **101**, 932.

It has been observed that the incidence or activation of peptic ulcers is high in patients treated with corticotrophin, cortisone, or hydrocortisone. Ulcers occurred in twelve (24 per cent.) of 49 patients being treated for rheumatoid arthritis with various corticosteroids. The case histories of the twelve patients in which ulcer occurred (usually with atypical symptoms) are summarized in a Table and six are reported in detail. The pain experienced by these patients was often atypical but was the most reliable clinical symptom. Occult blood in the stools was also a useful guide. The radiographic evidence of ulceration in the patients was often scanty, a crater being sometimes the only evidence of ulceration. Tenderness to palpation was often diminished or absent. Sometimes a deformed duodenum could be demonstrated; if this was found in a patient whose duodenum was normal before the institution of therapy with corticosteroids, it could be regarded as presumptive evidence of

an ulcer. The authors conclude that a high index of suspicion is warranted in the examination of a patient receiving corticosteroids and experiencing even vague epigastric pain and occult blood in the stools.

P. A. Nasmyth.

Interaction of the Rheumatoid Factor with Antigen-Antibody Complexes and Aggregated Gamma Globulin. EDELMAN, G. M., KUNKEL, H. G., and FRANKLIN, E. C. (1958). *J. exp. Med.*, **108**, 105. 5 figs, 21 refs.

The authors report a series of experiments undertaken at the Rockefeller Institute for Medical Research, New York, in an attempt to characterize further the intricate interactions between purified rheumatoid factor (R.F.) —now known to be a γ globulin with a sedimentation constant of 19 S—and antibodies and other γ globulins.

The isolation of R.F. from euglobulin fractions or precipitates obtained from the serum of four patients with rheumatoid arthritis is described, density gradient zone centrifugation being used to obtain 90 per cent. of the 19-S material. Evidence was obtained that the addition of the systems consisting of ovalbumin, human albumin, and human γ globulin with the corresponding rabbit antibodies, the precipitates being compared by determining their nitrogen content. Furthermore, an additional precipitate occurred on the addition of R.F. to the supernatant fluid removed after precipitation had taken place in the control series, indicating the reaction of R.F. with soluble antigen-antibody complexes. In the zone of excess antibody globulin, where there is no soluble antigen-antibody complex, no precipitation occurred as the result of the addition of R.F. No similar increase in precipitation by R.F. was noted in a horse anti-pneumococcus Type-III system. Heating R.F. to 56° C. for one hour reduced only slightly the potentiation of precipitation in an anti-human-albumin system, and prolonging the reaction time of the antigen-antibody system from 24 hours to 7 days at 4° C. had no significant effect. An approximate linear relationship was established between the nitrogen content of the precipitate produced by the addition of R.F. and the quantity of protein nitrogen in the antibody-antigen system.

Direct precipitation reactions occur between R.F. and heated γ globulin, this increase reactivity being known to be due to the aggregation of globulin complexes. An increase in reactivity of a similar nature was obtained by pre-treating the γ globulin with guanidine or a mixture of urea and mercaptoethanol, the effect of the latter being largely blocked by iodacetamide. Increased inhibition of the sheep-cell agglutination reactions was achieved by pre-treatment of Fraction II γ globulin by similar methods. Zone ultracentrifugation in a sucrose density gradient demonstrated that the activity in each of these preparations was due primarily to aggregated material with a sedimentation constant greater than 20 S. Insoluble denatured precipitated human γ-globulin preparations were found to adsorb R.F., which could be readily eluted from them in urea or acid buffers, the eluate containing 70 per cent. of a 19-S component.

The authors discuss their findings and conclude that they contribute little to the solution of the question whether R.F. is an antibody to γ globulin or a complement-like substance. All the evidence indicated that only large complexes with a sedimentation constant greater than 20 S were involved in interactions with R.F. The suggestion is made that R.F. might represent an antibody to an antigen-antibody complex.

Harry Coke.

Characterization of the "Reactant" (Gamma Globulin Factor) in the F II Precipitin Reaction and the F II Tanned Sheep Cell Agglutination Test. CHRISTIAN, C. L. (1958). *J. exp. Med.*, **108**, 139. 13 figs, 22 refs.

An investigation is reported from Columbia University College of Physicians and Surgeons and the Presbyterian Hospital, New York, into the nature of the γ-globulin component, or "reactant", which interacts in precipitin and haemagglutination reactions with the rheumatoid factor. This factor is itself a γ-globulin complex with a sedimentation constant of 19 S, and exists in the serum of patients with rheumatoid arthritis as a soluble complex with a 7-S γ globulin, the combination having a sedimentation constant of 22 S. The complex interacts in a number of "diagnostic" tests with the γ globulin of Cohn's Fraction (F II).

In the present investigation commercial pooled human F was fractionated by precipitation with sodium sulphate (0·36 to 1·18 M) into six fractions, labelled SS_1 to SS_6. In the ultracentrifuge SS_1 gave a curve with an asymmetrical peak, at a sedimentation constant of approximately 40 S, and SS_2 showed a fairly symmetrical component with a value of 30 S, while the remaining fractions contained no component heavier than 7 S. The hexose : nitrogen ratios of the fractions did not differ significantly from that of whole F II. Fractions SS_3 to SS_6 were heated to 63° C., after which they contained components heavier than 7 S.

In combination with rheumatoid sera Fractions SS_1 and SS_2 yielded large amounts of precipitate, which were even greater after the fractions had been heated, whereas Fractions SS_3 to SS_6 did not produce more precipitate than was formed spontaneously in the serum. The precipitin reactivity of whole F II was intermediate between those of the inactive fractions SS_3 to SS_6 and the strongly reactive fractions SS_1 and SS_2. The separated 30-S and 40-S components alone induced precipitation with rheumatoid sera. After precipitation the supernatants were shown to contain some 22-S material which could be progressively precipitated by the addition of more SS_1, the haemagglutination titre being reduced in parallel with the removal of the precipitate. The 7-S globulin isolated was demonstrated to have an inhibitory effect on these precipitin reactions, which probably accounts for a number of phenomena observed in precipitin reactions with whole F II. Fractions SS_1 and SS_2 strongly inhibited a positive F-II-tanned-cell agglutination system, as did whole F II, though to a lesser degree. Similarly, when Fractions SS_1 and SS_2 were used to coat or sensitize sheep erythrocytes a relatively low

concentration was found to be effective; incomplete sensitization was effected with SS_3, and no sensitization was obtainable with SS_4 to SS_6.

The "reactant" appears therefore to consist of molecular aggregates of γ globulin with sedimentation constants above 7 S and as high as 40 S. *Harry Coke.*

New Method for the Demonstration of the "Agglutinating Factor" in Rheumatoid Arthritis. (Nouvelle méthode de recherche du "facteur agglutinant" de la polyarthrite chronique évolutive.) DULONG DE ROSNAY, C., DU PASQUIER, P., and MOUSTARDIER, G. (1958). *Ann. Inst. Pasteur*, **95**, 23. 1 fig., 10 refs.

The latex fixation test described by Singer and Plotz (*Amer. J. Med.*, 1956, **21**, 888; *Abstr. Wld Med.*, 1957, **22**, 50) detects a specific agglutinating factor present in the blood of patients with rheumatoid arthritis by means of its ability to agglutinate particles of polyvinyl toluene latex coated with human γ globulin. The authors, working at the Faculty of Medicine, Bordeaux, have modified this test by mixing the reagents on a slide instead of incubating then in a tube, and by using a latex of higher mean particle diameter (1·17 μ) and of increased concentration (0·1 per cent). When agglutination produced by a serum dilution of 1 in 80 was taken as positive and that by a dilution of 1 in 40 as "borderline", the result of the test on 118 normal sera was negative in 117 and borderline in one; of 64 rheumatoid arthritic sera, 57 gave a positive and one a borderline result of 36 sera from patients with other osteoarticular diseases, all gave a negative result, except one from a case of multiple myelomatosis and one from a patient with hypergammaglobulinaemia. The result of the Waaler-Rose test on the same 64 rheumatoid arthritic sera was positive in 51 cases, doubtful in four, and negative in nine. The authors state that the modified test is more reliable and takes less time to perform.

Allan St. J. Dixon.

Contribution to the Study of the Mechanism of the Waaler-Rose Reaction. (Contribution à l'étude du mécanisme de la réaction de Waaler-Rose.) SHICHIKAWA, R., MAYEDA, A., and YASUDA, J. (1958). *Ann. Inst. Pasteur*, **95**, 30. 2 figs, 29 refs.

In the studies here reported from the University of Osaka, Japan, the authors found that the agglutination-activating factor (A.A.F.) present in the serum of rheumatoid arthritic patients did not influence the agglutination of human A or B cells by the naturally occurring iso-agglutinins, but did enhance their agglutination by human anti-A or anti-B immune agglutinins (produced by immunization with A or B blood-group-specific polysaccharides). The enhancement was especially marked when the immune serum was previously absorbed with the corresponding antigen to remove complete antibodies and leave incomplete antibodies. Rabbit anti-human globulin (Coombs serum) had the same action. In other tests A.A.F. and Coombs serum were found to enhance the agglutination of Group O Rh-positive cells by incomplete anti-D antibody but not by complete anti-D. Heating the antiserum to 70° C. for 30 minutes destroyed the agglutinating power of the A and B iso-agglutinins and reduced that of A and B immune agglutinins. It did not reduce the enhancing effect of A.A.F. or of Coombs serum. The authors conclude that A.A.F. affects immune antibodies but not naturally occurring antibodies, and that the difference is due to the presence in immune antibodies of incomplete antibodies whose action it enhances. *Allan St. J. Dixon.*

Involvement of the Heart in Rheumatoid Arthritis. (Über die Herzmitbeteiligung bei der primär chronischen Polyarthritis.) PÄRTAN, J. (1958) *Wien. Z. inn. Med.*, **39**, 225. 7 figs, 28 refs.

In this study reported from the Second Medical Clinic of the University of Vienna, the author analyses the incidence of cardiac damage in 620 cases of rheumatoid arthritis, having excluded a further eighty cases in which it appeared likely that existing cardiac damage was due to other causes. The sex incidence was approximately four females to one male, the patients' average age was 50·3 years, and the average duration of the illness 10·5 years. At the time of onset about one-third of the patients were under 40, one-third between 40 and 50, and one-third over 50 years of age. The evidence for cardiac damage was based on the electrocardiographic findings, which were definitely pathological in 246 cases and doubtful in 146, while a normal electrocardiogram was recorded in 228. A notable clinical finding was the virtual absence of valvular lesions, the commonest abnormalities being myocardial damage (126 cases) and endocarditis (81 cases), while in 42 cases there were various types of disturbance of conduction; infarction was diagnosed in nine cases.

Numerous Tables and Figures illustrate the further break-down of the material according to various criteria. It is of interest that even in the younger age groups there was a high incidence of abnormal electrocardiograms, while in regard to the older age groups (50 to 60 and over) a control study among 100 patients with osteo-arthritis showed a markedly lower incidence of abnormal electrocardiograms than among these older rheumatoid patients. A shorter duration of the malady, at least up to 10 years, was shown to have a slightly favourable effect on the incidence of cardiac abnormalities, whereas the severity of the condition had the opposite effect, at least in the more disabling stages of the disease. The effect of prolonged corticosteroid therapy on the cardiac manifestations was difficult to assess in view of the small number of patients (19) thus treated and the relatively short period of observation (6 to 18 months), but the author records his general impression that the prognosis was most favourable in cases treated with a combination of prednisone and ACTH (corticotrophin).

H. F. Reichenfeld.

Laryngeal Stridor in Rheumatoid Arthritis. DARKE, C. S., WOLMAN, L., and YOUNG, A. (1958). *Brit. med. J.*, **1**, 1279. 7 figs, 24 refs.

The authors describe five cases of laryngeal stridor

associated with advanced rheumatoid arthritis seen at the Royal Infirmary and the City General Hospital, Sheffield. In four instances the stridor was so severe that tracheotomy was necessary.

In the first case, that of a man aged 62 who had suffered from rheumatoid arthritis for 5 years, an emergency tracheotomy was required in order to relieve an obstruction of the respiratory tract. Signs of bilateral abductor paralysis of the larynx were revealed on laryngoscopy; the cricoarytenoid joint movements were unrestricted. Diffuse interstitial fibrosis of the lungs developed and the patient died suddenly from bronchopneumonia. At necropsy the cricoarytenoid joints were found to be fully mobile. Microscopical examination showed chronic inflammation of the subhyoid bursa and also of the synovial lining of the cricoarytenoid and cricothyroid joints. There was evidence of demyelination of the vagus and laryngeal nerves. At necropsy in another case the vagi and the superior laryngeal and recurrent laryngeal nerves showed demyelination with varicose swelling of the axis cylinders. These changes were attributed to ischaemic neuritis which had resulted from a rheumatoid type of arteritis of the vasa nervorum. No signs of polymyositis or focal disease were detected in the laryngeal muscles and there was no evidence of pressure palsy.

It is suggested that when laryngeal stridor occurs in rheumatoid arthritis the condition may be produced either by arthritis of the cricoarytenoid joints or by abductor paralysis due to nerve degeneration. Cases described in the literature have a common pattern, with the onset of obstruction of the respiratory tract in the 6th or 7th decade, but the exact cause of the stridor can be established only by histological examination.

A. Garland.

Synovial Fluid in Rheumatoid Arthritis. [Monograph, in English.] MÄKINEN, P. (1958). *Ann. Med. exp. Fenn.*, **36**, Suppl. 7, 1. 9 figs, bibl.

Kidney in Rheumatoid Arthritis. (Nerka w gośćcu pierwotnie przewlekłym.) MACKIEWICZ, S., PRZYBYL, L., CHODERA, A., and LEJA, Z. (1958). *Pol. Tyg. lek.*, **13**, 1364. 16 refs.

Rheumatoid Arthritis of the Feet. LOCKIE, L. M., and ROBINS, H. M. (1958). *J. med. Soc. N.J.*, **55**, 656.

Slide Latex-Fixation Test. A Simple Screening Method for the Diagnosis of Rheumatoid Arthritis. SINGER, J. M., and PLOTZ, C. M. (1958). *J. Amer. med. Ass.*, **168**, 180. 8 refs.

Appraisal of Serologic Reactions in Rheumatoid Arthritis. [In English.] SULKIN, S. E., and PIKE, R. M. (1958). *Int. Arch. Allergy*, **13**, 61. 37 refs.

Rheumatoid Diseases, Antimalarials (Chloroquine and Hydroxychloroquine) as Therapeutic Aids. CRAMER, Q. (1958). *Missouri Med.*, **55**, 1203. 1 fig., 23 refs.

Problem of "Disengagement" from Corticosteroids in Rheumatoid Arthritis (Use of Chlorpromazine). (Il problema dello "sganciamento" dai cortisonici nell'-artrite reumatoide (utilita della cloropromazina).) GALLI, T., CAVIGLIA, E., SOLARI, S., and PAVERO, A. (1958). *Reumatismo*, **10**, 253. 2 figs, 217 refs.

Function of the Digestive Organs in Patients with Rheumatoid Arthritis. (Czynność narzadu trawienia u chorych na gościec pierwotnie przewlekły.) ROSŁAWSKI, A., and GOETZ, B. (1958). *Pol. Tyg. lek.*, **13**, 1583. 11 refs.

(Osteo-Arthritis)

Observations on Osteo-Arthritis. WAINE, H. (1958). *Arthr. and Rheum.*, **1**, 454. 37 refs.

Contribution to the Study of Osteo-Arthritis of the Knee Joint. (Contribuiçao ao estudo clínico da osteo-artrite do joelho.) NAVA, P. (1958). *Hospital (Rio de J.)*, **54**, 435. 66 refs.

Experience with Adenosine-5-monophosphoric Acid in the Treatment of Osteo-Arthritis of the Spine. (Erfahrungen mit Adenosin-5-monophosphorsäure bei der Behandlung der Spondylosis deformans.) BRÜCKNER, C., and SIMON, J. (1958). *Ther. d. Gegenw.*, **12**, 505. 1 fig., 5 refs.

Treatment of Osteo-Arthrosis of the Spine. A Review of 119 Cases. RICH, W. G. (1958). *N.Z. med. J.*, **57**, 353. 3 figs.

(Spondylitis)

Rheumatoid Spondylitis: Manifestations and Management. LEFKOVITS, A. M., and THOMAS, J. R. (1958). *Ann. intern. Med.*, **49**, 89. 2 figs, 14 refs.

This paper reviews the clinical and radiographic features and the results of treatment obtained in 267 cases of "rheumatoid spondylitis" in male patients at the Veterans Administration Hospital, Memphis, Tennessee. The age of onset varied from 17 to 54 years, but in more than half the patients the disease began during the third decade. Of 201 patients in whose notes the appropriate information was recorded, 25 (12·4 per cent.) gave a history of arthritis in some other member of the family. Subjective signs of peripheral arthritis were present in 166 (62·8 per cent.) of 264 patients and objective signs of peripheral joint involvement in 113 (42·4 per cent.) of 266 patients. The onset of the disease was usually insidious, with recurrent bouts of low backache. In 23·5 per cent. of all cases the patient described pain of sciatic distribution with or without paraesthesiae. Most characteristic

were pain and stiffness occurring during the night or early morning, with relief after a period of activity.

In those patients with early disease and no obvious physical signs the authors used a variety of orthopaedic manœuvres (including Lasègue's test) to demonstrate minimal degrees of limitation of movement in the spine or hip-joints. With more advanced disease flattening of the lumbar spine, dorsal kyphosis, reduced chest expansion, tenderness over the sacro-iliac joints, and spinal rigidity were noticed. In 139 cases (55·5 per cent.) some degree of anaemia was present and in 57 (21·8 per cent.) the leucocyte count was over 10,000 per c.mm. The erythrocyte sedimentation rate was increased in 209 patients (81·9 per cent.), the highest value being 54 mm. in one hour [method not stated], and C-reactive protein was present in the blood of 23 of the 26 patients tested. Hyperglobulinaemia was found in nine out of 34 patients examined. All patients had radiological evidence of sacro-iliac joint involvement; the authors emphasize the difficulty of recognizing and interpreting early changes. Calcification of spinal ligaments was seen in 89 cases (33·3 per cent.) and spinal osteoporosis in 64 (23·9 per cent.). The full triad of Reiter's syndrome was present in only three cases (the arthritis affecting both spinal and peripheral joints), though thirteen patients (4·5 per cent.) had associated iritis. Psoriasis was present in five patients and 36 had congenital abnormalities of the vertebral column.

Therapeutic measures used included postural treatment, weight correction, breathing exercises, local application of dry or moist heat, and radiotherapy (600 to 750 r. to as many as five areas, with smaller doses for second and third courses). A few patients received short courses of hydrocortisone (50 to 100 mg. daily) or phenylbutazone (400 to 600 mg. daily). Aspiration, sometimes with hydrocortisone replacement (50 to 100 mg.), was carried out in cases of synovial effusion. Patients with osteoporosis received appropriate hormonal therapy, and many were fitted with spinal supports.

The results of treatment are analysed and discussed briefly [although it is not clear how soon after treatment the assessments were made]. The difficulty of evaluating progress is mentioned, the authors relying generally on subjective estimates in classifying the degree of improvement as excellent, good, or fair, according to defined criteria. A good or excellent response was obtained in 70 (73·7 per cent.) of 95 patients whose treatment did not include radiotherapy, and in 125 (75·7 per cent.) of 165 who did receive radiotherapy.

The authors point out, however, that no valid conclusions can be drawn from the comparison of the results in these two groups of patients, since most of them received various types of treatment, of which irradiation was only one. *M. Wilkinson.*

Ocular Lesions in Ankylosing Spondylitis. (Spondylitis ankylopoietica und Auge.) BLATZ, G. (1958). *Z. Rheumaforsch.*, **17**, 274. 6 figs, 47 refs.

The ophthalmological findings in 694 patients undergoing spa treatment for rheumatic disorders at the Rheumatic Clinic, Bad Elster, Germany, are analysed. Ankylosing spondylitis had been diagnosed in 121 of these patients. [The criteria for this diagnosis are not stated.] Errors of refraction and opacities of the lens were rather less common in the spondylitics than in the other patients, but evidence of iritis was much more frequent, being present in 26 cases (21·5 per cent.) compared with 0·5 to 4 per cent. in the other diagnostic groups. Of the patients with spondylitis, two had acute iritis at the time of examination, twelve had posterior synechiae, and in twelve the iritis had subsided without sequelae. Evidence of iridocyclitis was found in three cases and atrophy of the iris in two. The iritis had developed in some cases before and in others after the diagnosis of spondylitis had been made. No constant relationship between the severity of the arthritis and of the iritis was discovered. It is stated that no unusual incidence of intestinal-tract infections or raised antistreptolysin titres was found in the patients with iritis. Only in 10 per cent. of cases was there appreciable loss of vision as a late sequel. *G. Loewi.*

Peculiar Changes in the Muscles of Patients with Ankylosing Spondylitis. TRAUT, E. F., and PASSARELLI, E. W. (1958). *A.M.A. Arch. Path.*, **66**, 110. 4 figs, 20 refs.

The changes on the muscles of patients with ankylosing spondylitis were studied in sections of the gastrocnemius muscle obtained from seventeen male patients (aged 28 to 60 years), eight of whom had been bedridden for 5 to 40 years. In all the patients the sacro-iliac joint was said to be obliterated. In seven patients there was some localized muscle atrophy, with perivascular cellular infiltration in four. Peculiar spindle-shaped structures were seen in the muscle in six cases: these appeared to be intrafibrillar and consisted of whorls of fibres giving a tinctorial reaction for collagen together with some mononuclear cells. No such structures have been reported, and none were observed by the authors, in the muscles of patients with rheumatoid arthritis. [From the details given it is not possible to determine whether the latter lesions were found in the patients who had been immobile or had peripheral as well as spinal arthropathy.] *G. Loewi.*

Clinical and Radiographic Aspects of the Commoner Lesions of the Sacro-Iliac Joints. (Aspectos clínicos y radiográficos de las lesiones más frecuentes de las articulaciones sacroilíacas.) LOSADA, M., and SOTO, O. F. (1958). *Arch. argent. Reum.*, **21**, 71. 9 figs, 35 refs.

Rheumatoid Spondylitis without Rheumatoid Arthritis of Peripheral Joints: Relationship to Rheumatic Fever and Valvular Heart Disease. HOLLISTER, L. E., and ENGLEMAN, E. P. (1958). *J. chron. Dis.*, **8**, 334. 21 refs.

Infective Spondylitis. (Les spondylites infectieuses.) RAVAULT, P., LEJEUNE, E., RIFFAT, G., and LAMBERT, R. (1958). *J. Méd. Lyon*, **39**, 995. 17 figs, 147 refs.

(Miscellaneous)

Head and Neck Pain in Temporomandibular Joint Disease and Muscle Spasm. FREESE, A. S. (1958). *A.M.A. Arch. Otolaryng.*, **67**, 410. 34 refs.

Estimates of the frequency of degenerative diseases of the temporo-mandibular joint vary between 28 and 40 per cent. of all persons over 40 years of age, but as there is no uniform standard of diagnosis these figures cannot be accurately evaluated. The changes in the joint differ little from the degenerative changes found with increasing age in other joints when allowance is made for the fact that the articulating surfaces are covered by fibrous tissue instead of hyaline cartilage. The clinical importance of the condition is usually that the pain causes spasm of the mandibular muscles and that this spasm increases the damage, so that a vicious circle is set up. Moreover, mandibular spasm of emotional origin is not uncommon as the mandibular muscles are used in the expression of emotion, and such spasm, if continued long enough, can initiate changes in the joint. The author emphasizes the importance of psychotherapy in the treatment of such cases. Apart from this the treatment should consist in the correction of any malocclusion on bite and the relief of spasm by means of moist heat, analgesics, and sometimes muscle relaxants. Complete ankylosis seems to be almost unknown, and in general the prognosis is good. *F. W. Watkyn-Thomas.*

A Histological Study of Dupuytren's Contracture. (La maladie de Dupuytren. Étude histologique.) NÉZELOF, C., and TUBIANA, R. (1958). *Sem. Hóp. Paris*, **34**, 1102. 8 figs, 18 refs.

This communication from the Hôpital Cochin, Paris, reports the results of a histological study of material (fragments of fascia and digital nodules) from 25 cases of Dupuytren's contracture. The various staining procedures employed included haematoxylin-eosin-saffron, iron alum, periodic-acid-Schiff (P.A.S.), Masson's trichrome stain, and stains for iron, elastin, metachromasia, and reticulin.

The lesion takes the form of proliferation of the fibrous tissue of the palmar aponeurosis. The authors distinguish two forms of the lesion, which they describe as nodular and lamellar (*forme lamellaire*), although many transitional stages were observed. The nodular form is characterized by the presence of nodular masses of fibroblastic cells containing collagen fibres which stain intensely by the P.A.S. technique and show frequent metachromasia. The lamellar form shows a more regular structure, with few cells; the collagen fibres are thick and often hyalinized, give a negative P.A.S. reaction, and only exceptionally show metachromasia. The authors suggest that the nodular form may represent a relatively recent and still developing stage of the lesion and the lamellar an older and stabilized form. They conclude that although these studies throw no further light on the aetiology of the condition they do at least exclude the possibility of its being inflammatory, rheumatic, or degenerative in nature, and do nothing to sustain the hypothesis of its being a collagen disease.

H. A. Sissons.

Sacro-Iliitis in Reiter's Disease. OATES, J. K. (1958). *Brit. J. vener. Dis.*, **34**, 177. 2 figs, 1 table, 14 refs.

It is pointed out in this paper that sacro-iliac disease is common in Reiter's disease and that it may not be possible to demonstrate it radiologically. Recurring attacks of iritis may be present in these cases.

A. G. Cross.

Capsulitis of the Shoulder (Technique of Measurement of Movements and Clinical Applications). (Les capsulites de l'épaule (Technique de mensuration des mouvements et applications cliniques).) TROISIER, O. (1958). *Rhumatologie*, **10**, 113. 13 figs, 6 refs.

Intra-Articular Treatment in Acute and Chronic Arthritis. (Tratamiento intra-articular en las artritis agudas y crónicas.) SEMBER, J. (1958). *Rev. argent. Reum.*, **23**, 243.

"Durafoam"—A New Material for Rest Splints in the Prevention of Deformity in the Chronic Rheumatic Diseases. SWANSON, J. N. (1958). *Canad. med. Ass. J.*, **79**, 638. 3 figs, 6 refs.

Aetiological and Pathogenetic Considerations in Tietze's Syndrome. (Considerazioni etiopatogenetiche sulla sindrome di Tietze.) SCHIAVETTI, L., and GOSPODINOFF, A. (1958). *Reumatismo*, **10**, 161. 13 figs, 18 refs.

Tietze's Syndrome. ROBERTS, A. E. (1958). *Penn. med. J.*, **61**, 1497. 4 refs.

Disk Syndrome

Use of Contrast Media in the Presence of Low Back Pain and the Disk Syndrome. LEVERNIEUX, J. (1958). *Rheumatism*, **14**, 94. 4 figs, 19 refs.

Treatment of Sciatica due to Diskal Hernia by means of a Plaster Corset. (Tratamiento de la ciática "por hernia discal" mediante el corsé enyesado.) QUEROL, J. ROTES, and SANJURJO, L. A. C. (1958). *Rev. esp. Reum.*, **7**, 581. 9 refs.

Gout

Clinical and Nosological Relationship between Gouty Polyarthritis and Rheumatoid Disease. (Rapporti clinico-nosografici fra poliartropatia gottosa e malattia reumatoide.) LUCHERINI, T., and CERVINI, C. (1958). *Reumatismo*, **10**, 134. 10 figs, 64 refs.

Rheumatic Diseases and the Blood Uric Acid Level. (Malattie reumatiche e livello ematico dell'acido urico.) SCHIAVETTI, L., GOSPODINOFF, A., and VIOLANTI, A. (1958). *Policlinico, Sez. prat.*, **65**, 1725. 5 figs, 29 refs.

Contribution of Radiology to the Diagnosis of Gout. (Contribución de la radiología al diagnóstico de la gota.) HENDERSON, A. T., and TOPAZ, E. R. (1958). *Arch. argent. Reum.*, **21**, 118.

Radiology of Gout. (Radiología de la gota.) MIZRAJI, M., and CRESPO, I. (1958). *Rev. esp. Reum.*, **7**, 557. 19 figs, 45 refs.

Gout in the Negro Female. RODNAN, G. P., and GOLOMB, M. W. (1958). *Amer. J. med. Sci.*, **236**, 269. 6 figs, 14 refs.

Pararheumatic (Collagen) Diseases

Evaluation of the P-Toluene Sulphonic Acid Test for Systemic Lupus Erythematosus. [In English.] EKELUND, C. (1958). *Acta rheum. scand.*, **4**, 172. 1 ref.

The author, from the Hospital for Rheumatic Diseases, Spenshult, Sweden, reports an investigation of the value of a simple protein flocculation test originally described by Jones and Thompson (*J. Amer. med. Ass.*, 1958, **166**, 1424; *Abstr. Wld Med.*, 1958, **24**, 214), in the diagnosis of systemic lupus erythematosus, the test reagent being a 12 per cent. solution of *p*-toluene sulphonic acid in glacial acetic acid. The test was carried out with solutions containing various concentrations of the different serum protein electrophoretic fractions. A positive result was obtained only with solutions of gamma globulin of 1 per cent. or stronger.

Positive results were obtained with sera from seven out of ten patients with joint symptoms typical of rheumatoid arthritis and giving a positive response to the L.E.-cell test, 57 out of 165 patients with rheumatoid arthritis [and presumably a negative reaction to the L.E.-cell test], and two patients with myelomatosis and cirrhosis respectively. Of the 57 positive reactions in patients with rheumatoid arthritis, 35 were only weakly positive. The results of the test were negative with sera from nineteen patients with various other diseases and from thirty healthy subjects. In all specimens of sera giving a positive reaction to the flocculation test the gamma-globulin level was raised but in specimens which were negative to the flocculation test the gamma-globulin level was equally raised. The author concludes that this test does not differentiate lupus erythematosus from rheumatoid arthritis. *M. Wilkinson.*

Systemic Lupus Erythematosus simulating Acute Surgical Condition of the Abdomen. POLLAK, V. E., GROVE, W. J., KARK, R. M., MUEHRCKE, R. C., PIRANI, C. L., and STECK, I. E. (1958). *New Engl. J. Med.*, **259**, 258. 6 figs, 19 refs.

Since systemic lupus erythematosus (L.E.) affects small blood vessels throughout the body any or all of the organs may be involved. In this paper from the University of Illinois College of Medicine, Chicago, the authors describe fourteen cases in which the abdominal symptoms predominated to such an extent as to suggest an "acute surgical condition of the abdomen". In ten there was clinical evidence of local or generalized serositis, and in five necropsy or operation revealed involvement of the small arteries in the subserosa and submucosa. If the wall of the appendix or gall-bladder is involved the clinical picture is identical with that seen in patients without L.E. Pancreatitis was present in four patients and of these three died. In another case lesions of systemic L.E. were associated with those of polyarteritis nodosa—an association which has previously been reported. There is a tendency for the abdominal signs and symptoms to recur. The diagnosis may be difficult, but the presence of lesions in other organs, together with leucopenia or an abnormal urinary sediment, helps in differentiation. The intravenous administration of steroids usually results in improvement within 24 to 48 hours. *D. Preiskel.*

Pleuritis in Systemic Lupus Erythematosus: Its Importance as an Early Manifestation in Diagnosis. WINSLOW, W. A., PLOSS, L. N., and LOITMAN, B. (1958). *Ann. intern. Med.*, **49**, 70. 2 figs, 45 refs.

The authors describe the cases of two female patients presenting with a pleural effusion, both of whom gave a negative tuberculin reaction and positive L.E.-cell reaction. These cases stimulated the authors to review the clinical notes and radiographs of all cases of systemic lupus erythematosus in the records of the Montefiore and New York Hospitals, New York, since 1945. They were able to demonstrate that pleurisy was often an early feature of the disease in this series, whereas an extensive review of the literature suggested that it is usually regarded as a late manifestation.

The diagnosis of systemic lupus erythematosus was confirmed at necropsy in 23 of the 77 cases reviewed, and was based on clinical and laboratory findings in the remainder. Radiographs of the chest were available in 57 cases, and in 34 of these showed evidence of pleurisy, with or without effusion, while in seven others there was a history of pleuritic pain without *x*-ray evidence; only in eight of these cases were there complicating diseases likely to cause pleurisy. Pleurisy was the first manifestation of the disease in three of the uncomplicated cases in his group and was an "early" feature (that is, was preceded by only one other major manifestation) in sixteen others. The presence of radiographic or clinical evidence of pleurisy was also recorded in the notes of ten of the twenty cases in which radiographs were not available for review, complicating disease being present in one of the ten. There were thus 42 cases of pleurisy without complicating disease in the whole series. It is pointed out that this incidence is higher than that recorded in most published series.

In 32 of the uncomplicated cases the pleurisy occurred before the diagnosis of lupus erythematosus had been

made, arthritis or arthralgia being the most common preceding manifestation in these cases. Although coincidental pericarditis or pneumonitis occurred in a few cases, 21 of these 32 patients had at least one episode of pleurisy without detectable pneumonitis. The pleurisy was bilateral (simultaneous or alternating) in 23 of the 42 uncomplicated cases. In thirteen of the nineteen remaining cases the pleurisy was left-sided. The pleurisy showed a marked tendency to resolve, and of the 34 uncomplicated cases which were adequately followed up radiologically, complete clearing was seen after one or more episodes in fourteen, while minimal pleural residua persisted in eight. The average survival after the first pleuritic episode was 39·9 months, though one patient survived 17 years; 23 patients were alive at the time of the report, one of them 20 years after the onset of pleurisy.

The authors discuss the difficulty of making a clinical diagnosis of systemic lupus erythematosus and outline their criteria. They emphasize that this diagnosis should be considered in all cases in which there is unexplained pleurisy. *M. Wilkinson.*

Role of Mucinolysis in Collagen Disease. GESCHICKTER, C. F., ATHANASIADOU, P. A., and O'MALLEY, W. E. (1958). *Amer. J. clin. Path.*, **30**, 93. 20 figs, 5 refs.

After listing the main histo-pathological features common to the group of "collagen" diseases the authors describe a series of experiments, carried out at Georgetown University School of Medicine, Washington, D.C., in which they applied 2, 1, and 0·5 per cent. solutions of dimethyl*para*phenylenediamine to a shaved area of the skin (about 2 × 3 cm.) of rats, the object being to reproduce experimentally the lesions found in collagen diseases.

In the animals painted with the 2 per cent. concentration death occurred in about 12 days. Locally, the skin was ulcerated; in addition, the lungs were oedematous, the heart showed cellular aggregates resembling Aschoff bodies, there was superficial ulceration of the stomach, the adrenal glands were enlarged, and the spleen showed changes indicating diminution of lymphoid tissue. The rats treated with the 1 per cent. concentration died between 30 and 60 days later. In addition to the features described above there was also thickening of the walls of some of the small arteries. After application of the 0·5 per cent. solution some animals lived longer; in these the observed changes included endothelial proliferation of small blood vessels in the lung and some fibrinoid change in the heart, while the synovial membrane of the knee-joints showed collections of cells which the authors liken to the appearances in rheumatoid arthritis. Application of the 2 per cent. concentration for 2 to 4 days to the skin of very young rats produced glomerular changes which the authors describe as "wire-loops". The authors claim that the changes described are due to lysis of the matrix of connective tissue, a process which they allege to be a feature of collagen disease.

[In the abstracter's opinion the evidence presented in this paper is not very convincing.] *G. Loewi.*

Collagen Diseases of the Upper Respiratory Tract. ARSLAN, M. (1958). *Ann. Otol. (St. Louis)*, **67**, 279. 6 figs, 14 refs.

Research by the author and his colleagues at the Clinic of Otorhinolaryngology of the University of Padua has shown that certain primary conditions of the upper respiratory tract of hitherto unknown aetiology present clinical and pathological features identical with, or similar to, those of the systemic collagen diseases. Moreover, in many cases there are associated generalized connective-tissue changes, without clinical manifestations, in other parts of the body.

The chief condition of this type is the granuloma gangraenescens or malignant granuloma of the nose, in which there appear in the arteries changes resembling those of polyarteritis nodosa or of Buerger's disease. In all the cases studied biopsy of muscle and subcutaneous tissue from the limbs showed characteristic changes in the muscle fibres and arterioles, even though there were no extranasal symptoms. Other diseases in which local changes have consistently been found to be associated with generalized lesions suggestive of collagen disease are the Gougerot-Sjögren syndrome and collagenosis of the auricle and nasal cartilages. The histological appearances in amyloidosis of the larynx suggest its inclusion in the same group, although no generalized changes have been demonstrated. On the other hand muscle biopsy has given positive results in cases of ozaena and allergic ethmoidal polyposis, although the histology of the local lesions is not characteristic of collagen disease.

External carotid arteriography is suggested as an aid to the diagnosis of granuloma gangraenescens, the arteriogram showing a reduction in the lumen of the vessels supplying the affected area. Two patients with this disease have been subjected to cervical sympathectomy, with complete recovery lasting for many years.

William McKenzie.

Disseminated Lupus Erythematosus, Scleroderma, and Dermatomyositis as Manifestations of Sensitization to DNA-Protein. I. An Immunohistochemical Approach. BARDAWIL, W. A., TOY, B. L., GALINS, N., and BAYLES, T. B. (1958). *Amer. J. Path.*, **34**, 607. Bibl.

The authors, working at Harvard Medical School and St. Margaret's and the Robert Breck Brigham Hospitals, Boston, have used the fluorescent antibody method in studying sera obtained from cases of disseminated lupus erythematosus (6), scleroderma (6), dermatomyositis (2), rheumatoid arthritis (8), acrosclerosis (1), temporal arteritis (2), and miscellaneous conditions such as glomerulo-nephritis, penicillin reaction, hydatid mole, eclampsia, and normal pregnancy. L.E. cells had been found in the five active cases of lupus and in four of the cases of rheumatoid arthritis. The serum globulin fractions were conjugated to fluorescein *iso*cyanate and sections of normal human or rabbit tissues treated with the conjugates.

Tissue nuclei were found to stain with γ-globulin conjugates from the active cases of lupus, scleroderma, and dermatomyositis, from five of the cases of rheumatoid arthritis, and the case of acrosclerosis. No staining

occurred with conjugates from the other sera, with the sole exception of nuclear staining of rabbit myocardium with serum from a case of temporal arteritis. Staining could be prevented by treating the sections with deoxyribonuclease, but not by treatment with ribonuclease. The material responsible for staining was therefore presumed to be deoxyribonucleoprotein. Staining with conjugated serum was inhibited by previous treatment of the sections with unconjugated serum from the same source. Cross-inhibitions were observed between certain of the active sera, but were complex and not analysed in detail.

The authors conclude that in disseminated lupus erythematosus, scleroderma, and dermatomyositis the serum contains one abnormal γ-globulin factor, probably an antibody, which combines with intranuclear deoxyribonucleoprotein. They suggest that these diseases and perhaps rheumatoid arthritis, may be due to sensitization to intrinsic or extrinsic nucleoprotein.

[Substantially the same findings in disseminated lupus erythematosus were reported by Holborow *et al.* (*Brit. med. J.*, 1957, **2**, 732; *Abstr. Wld Med.*, 1958, **23**, 75).]

M. C. Berenbaum.

L.E. Phenomenon and Systemic Lupus Erythematosus. Louis, J., and Limarzi, L. R. (1958). *J. chron. Dis.*, **8**, 596. 2 figs, 30 refs.

Systemic Lupus Erythematosus. McCarthy, T. F., and Misra, D. P. (1958). *Postgrad. med. J.*, **34**, 592. 11 refs.

Systemic Lupus Erythematosus: A Clinical Report of 47 Cases with Pathological Findings in Eighteen. Copeland, G. D., Capeller, D. von, and Stern, T. N. (1958). *Amer. J. med. Sci.*, **236**, 318. 1 fig., 24 refs.

Symptomatology of Disseminated Lupus Erythematosus. (Sintomatología del lupus eritematoso diseminado.) Losada, M., Chamorro, G., Klinger, J., Zañartu, J., Donoso, H., Etcheverry, R., Guzman, C., and Katalinic, V. (1958). *Arch. argent. Reum.*, **21**, 106. 14 refs.

Clinical and Pathological Aspects of the Disseminated Lupus Erythematosus Syndrome. Chamorro, G., Barahona, R., Losada, M., and Silva, L. (1958). *Arch. interamer. Rheum.*, **1**, 288. 11 refs.

Renal Involvement in Schönlein-Henoch Disease. (L'interessamento renale nella malattia di Schönlein-Henoch.) Cavazzuti, G. B. (1958). *Minerva nefrol.* (*Torino*), **5**, 147. 27 refs.

Clinical and Morphological Considerations in Digestive Disorders associated with Collagen Diseases. (Considérations clinico-morphologiques sur les troubles digestifs dans les maladies du collagène.) Stoia, I. (1958). *Rhumatologie*, **10**, 143.

The Lung and the Collagen Diseases. (El pulmon y las colagenopatias.) Moro, E. R. de (1958). *Pren. méd. argent.*, **45**, 1997. 6 figs, 27 refs.

The Problem of Arthritis and Psoriasis. Rosenberg, E. F. (1958). *Illinois med. J.*, **114**, 201. 7 figs, 19 refs.

General Pathology

Erythrocyte Sedimentation Rate and Erythrocyte Sedimentation Curve in clinically Healthy Children in Creches, Kindergartens, and Schools. [In Russian.] Ionova, I. A. (1958). *Pediatriia*, **36**, 62. 8 refs.

The author has studied the effect of a 2-month summer holiday in the country on the erythrocyte sedimentation rate (E.S.R.) and the sedimentation curve in a group of clinically healthy Moscow children. The sedimentation curve was constructed by Epstein's method, the fall of the erythrocyte column [? Westergren's technique] being noted every 15 minutes for 1½ to 2 hrs and plotted against time. According to Steinberg, there are five characteristic types of curve:

(1) Hyper-reactive, with the greatest fall in the 1st two 15-minute periods, typical of acute infections when resistance is high;

(2) Reactive, with the greatest fall in the 3rd period, found in acute infections with adequate resistance;

(3) Hyporeactive, with the greatest fall in the 4th and 5th periods, typical of convalescence and of acute infections when resistance is low;

(4) A reactive, a flat curve with a fall of 0·5 to 1 mm. every 15 minutes, found in cases with markedly low resistance;

(5) Normal, a curve of diminishing slope which approaches the horizontal in its second half.

The children observed were drawn from creches, kindergartens, and schools and ranged in age from less than one up to 10 years. Readings were obtained before the holiday from ninety children (divided into five age groups), of whom fifty were under and forty over 4 years of age. Of this number, 66 were re-examined after the holiday; 46 of these were under 4 and twenty between 4 and 7, none of the twenty children aged 7 to 10 in the original group being re-examined. All the older children were well nourished and had had no recent illnesses, but a few of the younger ones were slightly undersized. Most of the infants under one were bottle-fed. A large proportion of the remainder had suffered from rickets in infancy, most of them having been bottle-fed and

many living in an unsatisfactory environment and getting little fresh air during the winter months. Each age group included both completely healthy children and children with a very mild degree of rhinitis or bronchitis.

The E.S.R. and sedimentation-curve findings before and after the holiday are analysed in a series of tables. Before the holiday the E.S.R. was more than 12 mm. in 1 hour in 27 of the fifty children under 4, while the curve was of Type 1 or 2 in 25 and of Type 5 in the other 25. After the holiday only four of the 46 children under 4 examined had an E.S.R. over 12 mm. in 1 hour and only four curves of Type 1 or 2 were obtained, though fourteen were of Types 3 or 4. Of the forty children aged 4 to 10 examined before the holiday, eleven had an E.S.R. over 12 mm. in 1 hour and the same number had curves of Type 1 or 2, with five of Types 3 or 4. After the holiday only two out of twenty children aged 4 to 7 had a raised E.S.R., while five had curves of Type 3, all the others being normal.

It is concluded that, although none of these children was clinically ill, the findings indicate that their sojourn in the country had improved their state of health.

Margot C. Dunlop.

Effects of Sodium Citrate and Potassium Ammonium Oxalate on the Erythrocyte Sedimentation Rate. [In English.] EASTHAM, R. D., DENSON, K. W. E., and EVANS, D. A. (1958). *Acta med. scand.*, **161**, 277. 4 figs, 23 refs.

Sodium citrate causes shrinkage of the red cells, shortening of the duration of the phase of aggregation, and diminution both in the rate and the duration of the phase of maximum sedimentation, when compared with the effect of the oxalate mixture. The variation in each phase is less when sodium citrate is used than when potassium-ammonium oxalate is used, thus it is suggested that the Westergren method is the more satisfactory of the two. The duration of the phase of aggregation is inversely proportional to the maximum sedimentation rate, and directly proportional to the haematocrit. The height of the supernatant plasma column at the onset of the phase of packing is inversely proportional to the haematocrit, and directly proportional to the maximum sedimentation rate.

No advantage was found in favour of routine estimation of the maximum erythrocyte sedimentation rate as compared with the simpler reading of the blood column at one hour, except possibly in the serial study of blood samples with very rapid sedimentation rates. There appeared to be no advantage in reading the column height at 45 minutes instead of at 60 minutes.

The Westergren and Wintrobe methods cannot be compared quantitatively.—[*Authors' summary.*]

"Periston" Latex-Fixation Test in the Diagnosis of Rheumatic Diseases. (Der "Periston-Latex-test" zur Diagnose rheumatischer Erkrankungen.) WIEDERMANN, G., EGGHARDT, F., and BRAUNSTEINER, H. (1958). *Z. Rheumaforsch.*, **17**, 314. 12 refs.

The authors describe a method of testing the euglobulin fraction of the serum protein for the presence of rheumatoid factor by the latex-fixation method of Singer and Plotz (*Amer. J. Med.*, 1956, **21**, 888; *Abstr. Wld Med.*, 1957, **22**, 50). In practice 1 ml. serum is mixed with an equal part of 20 per cent. saline, centrifuged, and the deposit dissolved in glycine buffer at *p*H 8·2, serial dilutions being used in the test in place of serum. Of ten sera from established cases of rheumatoid arthritis which had given negative results with the standard technique, eight gave positive results with the authors' technique. Of 21 control sera, two gave a positive result; both these sera came from patients with cirrhosis of the liver, a condition which has been found to give positive readings with other methods.

[The euglobulin fraction has previously been successfully employed in the Waaler-Rose test by Ziff *et al.* (*Amer. J. Med.*, 1956, **20**, 500; *Abstr. Wld Med.*, 1956, **20**, 387), and Svartz and Schlossmann (*Acta med. Scand.*, 1954, **149**, 83 and *Nord. Med.*, 1954, **51**, 668; *Abstr. Wld Med.*, 1954, **16**, 406) have used a fraction obtained by a cold precipitation method in the same test. The advantages of the present modification appear to be speed and simplicity.] *G. Loewi.*

Latex-Fixation and L.E.-Cell Tests. Studies of Their Diagnostic and Aetiological Significance in Rheumatoid Arthritis. (Der Latex-Fixationstest und der Lupus erythematodes-Zellentest.) BRAUNSTEINER, H., EGGHART, F., REINHARDT, F., and WIEDERMANN, G. (1958). *Dtsch. med. Wschr.*, **83**, 2168. 34 refs.

Changes in the Proteins, Glycoproteins, and Lipoproteins in Synovial Fluid on Standing and in the Presence of Hyaluronidase. (Variations des protéines et des glyco- et lipoprotéines dans les liquides synoviaux en fonction du temps et en présence d'hyaluronidase.) DE TRAVERSE, P. M., COQUELET, M. L., DEPRAITERE, R., FORESTIER, J., FORESTIER, F., and DESLOUSPAOLI, P. (1958). *Acta rheum. scand.*, **3**, 157. 4 figs, 10 refs.

Immunohistochemical Analysis of Lesions associated with "Fibrinoid Change". VAZQUEZ, J. J., and DIXON, F. J. (1958). *A.M.A. Arch. Path.*, **66**, 504. 24 figs, 36 refs.

Creatinuria in Patients with Rheumatoid Arthritis. (Kreatinurie bei Kranken mit primär chronischer Polyarthritis.) KOVÁCS, L., and VIDA, M. (1958). *Z. Rheumaforsch.*, **17**, 366. 18 refs.

Recent Immuno-Electrophoretic Investigations of the Serum of Patients with Rheumatism. (Neuere immunoelektrophoretische Untersuchungen im Serum Rheumakranker.) CLEVE, H. (1958). *Z. Rheumaforsch.*, **17**, 350. 4 figs, 45 refs.

Serological Studies of Rheumatoid Arthritis. [In English.] SHIMIZU, G'I., SHICHIKAWA, K., and TANABE, S. (1958). *Acta rheum. scand.*, **4**, 145. 4 figs, 15 refs.

Serum Complement in Connective Tissue Disorders. WILLIAMS, R. C., and LAW, D. H. (1958). *J. Lab. clin. Med.*, **52**, 273. 6 figs, 20 refs.

Sensitized Sheep Cell Haemagglutination Reaction in Rats with Experimental Infection of Bone and Joint. LERNER, E. M., II, WILLIAMS, R. R., and JENKINS, J. C. (1958). *Proc. Soc. exp. Biol. (N.Y.)*, **90**, 249. 1 fig., 24 refs.

Quantitative Considerations of the Rheumatoid Factor. VAUGHAN, J. H., ELLIS, P. J., and MARSHALL, H. (1958). *J. Immunol.*, **81**, 261. 6 figs, 26 refs.

ACTH, Cortisone, and Other Steroids

Metabolism of Cortisol by Loose Connective Tissue *in vitro*. BERLINER, D. L., and DOUGHERTY, T. F. (1958). *Proc. Soc. exp. Biol. (N.Y.)*, **98**, 3.

Fourteen mice were killed by decapitation, and connective tissue collected from them was distributed among eight incubation flasks. Each flask contained 0·3-0·6 g. tissue in 10 ml. 0·1 M phosphate buffer, *p*H 7·4, and cortisol 4-C^{14} (25,000 c.p.m.; specific activity 1·467 μ/mole). The flasks were shaken for 4 hrs in a water bath at 37° C. Two control flasks were incubated without tissue and two control flasks with tissue were not incubated. After the incubation period, the contents of the flasks were extracted with acetone. The extract was evaporated under a stream of nitrogen and the remaining aqueous phase was extracted with chloroform. The chloroform fraction was evaporated and chromatographed in the chloroform/formamide system of Zaffaroni. In the incubated and non-incubated control flask only cortisol was present, but on chromatograms made from the material in the test flasks five peaks of radioactivity occurred from which six compounds were identified and one compound was isolated but not identified. The identified metabolites were 20-epi substance E of Reichstein; cortisone; dihydro cortisol; corticosterone; and 4-androstene, 11 beta-ol, 3, 17-dione, and unmetabolized cortisol. 90 per cent. of the cells in the connective tissue used in the experiments were fibroblasts and the relationships of the metabolic picture produced to the fibroblastic role on the anti-inflammatory action of cortisol is discussed. *P. A. Nasmyth.*

Effect of Cortisol on Gastric Ulcers of the Shay Rat. ROBERT, A., and NEZAMIS, J. E. (1958). *Proc. Soc. exp. Biol. (N.Y.)*, **98**, 9.

98 female rats were divided into groups of eight to ten animals. All the animals were fasted for 48 hours, but at the commencement of the fasting period half of them were given 10 mg. cortisol suspension subcutaneously. The other half were used as controls and received subcutaneously 0·2 ml. of the vehicle in which the cortisol was suspended. These injections were repeated every 24 hours. At the end of the fasting period the pylorus was ligated using Shay's method, or alternatively a sham operation was performed. Groups of animals were killed 3, 6, 9, 10, and 12 hrs after the operation, and the stomachs were removed and inspected for ulcers. The volume of the accumulated gastric juice was also measured. No ulcers had appeared in the sham-operated rats 10 hrs after the operation, nor were there any ulcers 3 hrs after ligation of the pylorus. After 3 hrs the incidence of rumenal ulcers and perforations increased up to 12 hrs in the control animals given injections of the vehicle. Fewer rumenal ulcers and perforations occurred in the animals given cortisol. The volume of gastric juice secreted did not appear to be affected by the cortisol. However, the cortisol did promote the formation of ulcers in the corpus of the stomach whether or not the pylorus was ligated. *P. A. Nasmyth.*

Effects of Cortisol and Phenylbutazone on Experimental Arthritis and Serum Polysaccharide/Protein Ratios in Rats. HERSHBERGER, L. G. (1958). *Proc. Soc. exp. Biol. (N.Y.)*, **90**, 55. 1 fig., 10 refs.

Hypoglycaemic Incidents during the Treatment of Chronic Polyarthritis with Cortisone. (Hypoglykaemisches Vorkommen während Cortison-Kuren bei chronischen Polyarthritikern.) GÁSPÁRDY, G., and VIDA, M. (1958). *Z. Rheumaforsch.*, **17**, 387. 4 figs, 17 refs.

Effect of Cortisone on Connective Tissues of the Rat. SOBEL, H., GABAY, S., and JOHNSON, C. (1958). *Proc. Soc. exp. Biol. (N.Y.)*, **99**, 296. 12 refs.

Adrenocortical Reserves and the Sex Difference of Adrenocortical Excretion in Patients with Rheumatoid Arthritis. [In English.] PEKKARINEN, A., and KALLIOMÄKI, L. (1958). *Acta endocr. (Kbh.)*, **28**, 417. 39 refs.

Other General Subjects

Roentgenologic Changes of the Skeletal System in Cushing's Syndrome. HOWLAND, W. J., PUGH, D. G., and SPRAGUE, R. G. (1958). *Radiology*, **71**, 69. 5 figs, 18 refs.

The authors have reviewed the radiographs of the skeleton of 141 patients with a clinical diagnosis of Cushing's syndrome seen at the Mayo Clinic. Since, however, they were especially interested in an unusual

condensation of the margins of some collapsed vertebral bodies associated with this condition, only 69 cases in which a lateral view of the spine was available were completely analysed; the radiographs of fifty patients with severe generalized osteoporosis from other causes were compared as a control.

Of the radiographs of the skull of 43 patients with Cushing's syndrome, 41 showed osteoporosis; in 25 this was of a diffuse type and in eighteen of a "metastatic-appearing" type manifested by irregular zones of rarefaction. Radiographs of eleven of these patients in clinical remission for more than 6 months after treatment showed that the osteoporosis was unchanged in three, improved in six, and disappeared in two. In three cases metastatic areas had recalcified, but seven showed enlargement and erosion of the sella and in a number of instances there was sellar decalcification. In thoracic films, which were available for 55 patients, osteoporosis was present in all but one, fractures of the ribs being frequent and multiple, while the reparative callus was usually heavy. In forty controls, osteoporosis was present in every instance, but fractures of the ribs had occurred in only two, both of which had a history of trauma; here callus formation was normal. All but two of 68 radiographs of the pelvis showed osteoporosis, and fractures were present in six cases, with heavy callus formation; in contrast, in 46 controls all showing osteoporosis, there were no fractures. Of eleven radiographs of the extremities, four showed mild or moderate and one severe osteoporosis.

In the radiographs of the spine (all 69 cases) marginal condensation was present in 29 (53 per cent.) of the 55 cases showing severe or moderate osteoporosis. The condensation usually occurred along the upper margin of the vertebra, where there was readily apparent compression of the body. Of nineteen patients examined after treatment, eight showed a significant decrease in the degree of osteoporosis; of eight of these patients in whom condensation was also present, in two it had not changed, in three it had decreased, and in three it had disappeared completely. In the control group, compression fractures of one or more vertebral bodies, chiefly in the lower thoracic and upper lumbar regions, were present in 46 of the fifty radiographs available, but condensation of the vertebral body was found in only one case.

It is stated that marginal condensation of vertebral bodies in association with compression fractures has not been described hitherto in Cushing's syndrome. The authors consider that marginal condensation can occur in conditions other than Cushing's syndrome, but that it is minimal and rare. It has been reported by Sissons that photomicrographs of affected areas showed that slender trabeculae had become impacted and surrounded by new bone to form a thicker structure. Treatment with adrenocorticosteroids interferes with the healing of fractures and the callus formed does not give normal strength; these fractures are not so painful as usual owing to an analgesic action of the steroids, and for this reason the part is not splinted as much as it normally would be. There is thus a continued strong stimulus to excessive formation of osteoid, which becomes calcified. This may account for the marginal condensation of the vertebral bodies and the excessive callus formation around fractures. *John H. L. Conway-Hughes.*

Experience in the Management of Joint and Soft Tissue Disease with a New Form of Hydrocortisone for Local Injection. COODLEY, E. L. (1958). *J. chron. Dis.*, **7**, 429. 23 refs.

The author first briefly reviews some of the literature on the treatment of disease of the joints and bursae by intra-articular injection of steroid compounds and then reports from the Cedars of Lebanon Hospital, Los Angeles, the results obtained with concentrated preparations of hydrocortisone, 150 or 200 mg. of this steroid in 1 ml. being the usual dose injected into the joints. The 56 patients studied were suffering from various diseases including rheumatoid arthritis, osteo-arthritis, gout, bursitis, and tenosynovitis. In most cases the lesions were chronic and other forms of treatment had already been tried, while in some it was possible to compare the effect of the new treatment with the results obtained with the more usual smaller doses of hydrocortisone (50 mg. per ml.).

The results, which were evaluated subjectively, by clinical examination, and in a few cases by study of C-reactive protein reactions, showed that the over-all incidence of improvement resembled that previously reported from the use of the usual doses of steroids. Certain joints, however, showed unusually good results, improvement being noted in all elbows treated, 87 per cent. of knees, 83 per cent. of ankles, and 73 per cent. of shoulders. The benefit obtained was also of longer duration, improvement lasting 11 days or more in 40 per cent., as compared with 30 per cent. of the cases given the lower doses of steroids. Side-effects, both local and systemic, of steroid therapy occurred but were minimal. The author concludes that concentrated intra-articular injections of hydrocortisone produce somewhat better results than conventional doses, especially in resistant cases of tenosynovitis, chronic bursitis of the shoulder and elbow, and post-traumatic lesions.

M. Kendall.

Type, Mechanism, and Treatment of Weather Effects in Rheumatic Subjects. (Art, Wirkung und Behandlung von Wetterbeschwerden beim Rheumatiker.) WESKOTT. H. R. A. (1958). *Medizinische*, No. 43, 1713. 2 refs.

Experimental Researches on the Metabolic Activity of Sodium Salicylate. (Richerche sperimentali sulla attivitá metabolica del salicilato di sodio.) PICCINELLI O., and NICROSINI, F. (1958). *Arch. Sci. med.*, **105**, 369. 1 fig., 94 refs.

Observations on the Side-Effects of ACTH and Irgapyrine in the Treatment of Rheumatism. (Spostrzeznia nad ubocznym działaniem ACTH i irgapiryny w leczeniu gośćca.) JASIŃSKI, K. (1958). *Pol. Tyg. lek.*, **13**, 1628, 32 refs.

Critical Study of the Focal-Sepsis Theory of Rheumatic Disease. (Kritisches zur Fokallehre rheumatischer Erkrankungen.) SCHMID, J. (1958). *Klin. Med. (Wien)*, **18**, 370. 6 figs.

Rheumatoid Syndromes in the Malignant Blood Diseases. (Síndromes reumatoideos en las hemopatías malignas.) ETCHEVERRY B, R., GUZMÁN L, C., REGONESI L, C., MURANDA R, M., and LOSADA L, M. (1958). *Arch. argent. Reum.*, **21**, 96. 11 refs.

CORRIGENDA

In the article by J. Richmond, L. M. H. Roy, D. L. Gardner, W. R. M. Alexander, and J. J. R. Duthie, entitled "Nature of Anaemia in Rheumatoid Arthritis. IV" (*Annals*, 1958, **17**, 406):

p. 408, col. 1, l. 6: the haemoglobin standard should read 14·8 g./100 ml. and not 14·3.

p. 411, Table VIII: the iron content of bone marrow, as measured by the chemical method (cols 4 and 5), should be stated in mg./100 mg. protein and not in mg./g.

Ann. Rheum. Dis. (1959), **18**, 91.

TREATMENT OF RHEUMATOID ARTHRITIS BY A SANATORIUM REGIME

THE BLACK NOTLEY EXPERIMENT

BY

R. M. MASON AND W. G. WENLEY

The London Hospital

In 1954, as a direct result of the recommendations of the Royal College of Physicians Committee on Chronic Rheumatic Diseases (1951), the North-East Metropolitan Regional Hospital Board initiated a regional scheme for the treatment of this group of diseases. This involved a Central Regional Rheumatism Centre at the London Hospital with peripheral centres elsewhere in the Region. One of these was at a sanatorium (Black Notley Hospital, Braintree), which had beds available because of the reduced demand for sanatorium treatment of bone and joint tuberculosis. A small unit comprising ten beds for female patients in the care of Mr. M. C. Wilkinson and Dr. W. S. Tegner was therefore set up as a pilot experiment to study whether the treatment of rheumatoid arthritis by sanatorium methods was likely to make a useful contribution to the management of this disease.

Since this time we have admitted suitable cases from the London Hospital to this unit. The patients have been treated on standard sanatorium lines, with prolonged rest in bed, as much out of doors as possible, and with suitable splinting. Specific drug therapy, other than routine analgesics and iron, was not given, and steroid administration was discontinued in those cases who had previously been receiving these substances. Physiotherapy and other rehabilitation procedures were limited to the last few weeks of the stay in hospital, both because this was in line with previous sanatorium practice and because facilities were limited. A control group was formed of patients admitted to beds in the rheumatism unit at the London Hospital; a random selection of patients for admission to Black Notley was impracticable, because the number of those who would accept admission to a hospital in the country often some 50 miles away from their homes and families for many months was barely sufficient to fill the available beds, let alone to provide an equal number of controls. This attitude is an important factor and contrasts with the willingness to accept sanatorium treatment for tuberculosis. Clearly, if it could be shown that such a regime was worthwhile for certain categories of rheumatoid arthritis, this resistance might be overcome. It is the purpose of this report to examine whether there is evidence to encourage us to take such a view.

Clinical Material

To date forty patients have been admitted to the Unit, 38 of them for a period of 4 months or more. Of these, all but one (who went abroad and has been lost sight of) have been followed up. The average follow-up time was 17 months (range 6 to 46 months). Two patients discharged themselves soon after admission because they would not accept the regime required, and they have been excluded from the analysis of the results.

(*a*) *Type of Case Admitted.*—Patients whom we considered to have severe progressive disease with a bad prognosis, and for whom prolonged hospitalization seemed the only hope, and who were prepared to accept sanatorium treatment made up the number of cases admitted. They are compared with cases admitted to the beds under our care in the London Hospital during the same period and, where applicable, to other series of cases of rheumatoid arthritis in the literature.

TABLE I

PATIENTS ADMITTED TO BLACK NOTLEY COMPARED WITH LONDON HOSPITAL IN-PATIENTS (FEMALE) DURING THE SAME PERIOD, AND WITH EDINBURGH AND BOSTON SERIES

Series	No. of Patients	Mean Age on Admission (yrs)	Mean Duration of Disease (yrs)	Mean Age at Onset (yrs)
Black Notley	40	51·7	9·4	42·3
London Hospital (In-patients) ..	62	48·3	7·5	40·8
Duthie, Thompson, Weir, and Fletcher (1955)	205	50·5	7·3	43·5
Short, Bauer, and Reynolds (1957) ..	186	43	5·1	37·9

(*b*) *Age on Admission* (Table I).—The mean age on admission was 51·7 years. There were an equal number in the 41-50 and 51-60 decades which together form three-quarters of the total material (Fig. 1). During the same period we admitted to the beds in the London Hospital 62 female patients who were slightly younger (mean age 48·3 years). Our series at the sanatorium is strictly comparable to that reported by Duthie, Thompson, Weir, and Fletcher (1955) of 205 female cases admitted to the Rheumatism Unit in Edinburgh (mean age 50·5 years); in the Boston series (Short, Bauer, and Reynolds, 1957) of 186 females admitted to the medical wards of the Massachusetts General Hospital between 1930-1936 the mean age was 43 years. The mean age of the patients selected for the Empire Rheumatism Council Aspirin-

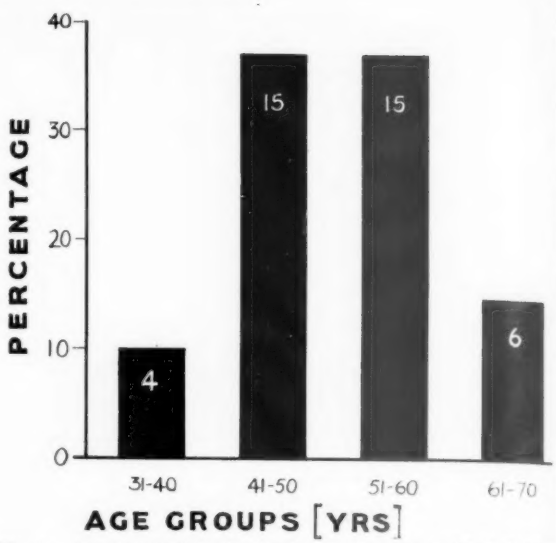

Fig. 1.—Age distribution of patients on admission to Black Notley.

Cortisone Trials (1955, 1957), which included both males and females and was essentially an out-patient study, was 48·3 years. Our patients, therefore, were representative so far as age is concerned of the usual hospital rheumatoid arthritis population, the mean age being slightly higher than that of those admitted for short periods of treatment into our general wards.

(*c*) *Duration of Disease* (Table I).—The mean duration in the Black Notley group was 9·4 years; the distribution is illustrated in Fig. 2. This shows that nearly all the patients had had symptoms for more than one year and that 60 per cent. had

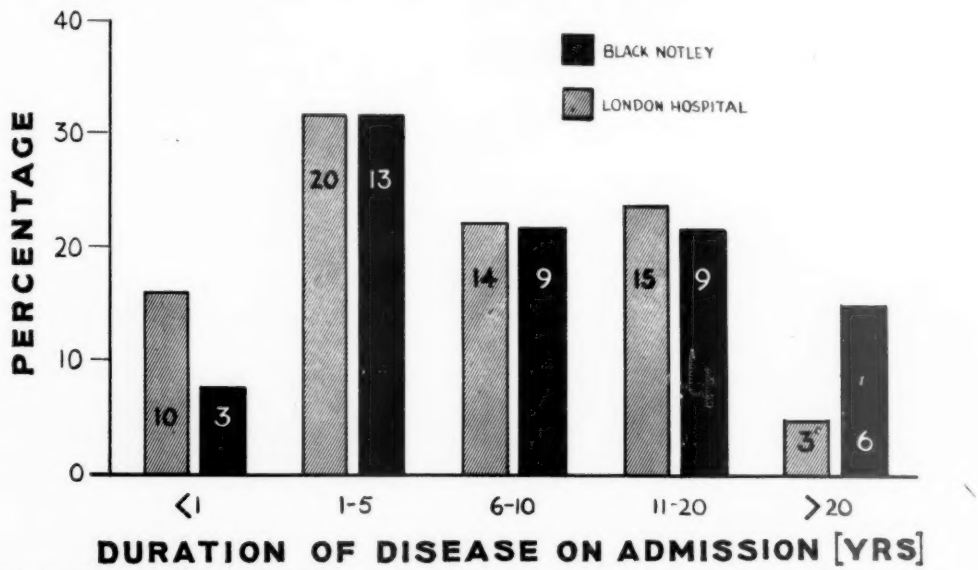

Fig. 2.—Duration of disease before admission to hospital in two series of patients (London and Black Notley).

had the disease for 6 years or more. The 62 female patients admitted to our beds in the general wards had a mean disease duration of 7·5 years; 52 per cent. of this group had had arthritis for 6 years or more. A disease duration of less than one year, however, was twice as frequent (16 per cent. compared with 8 per cent.), and only 5 per cent. had a disease duration of 20 years or more, compared with 15 per cent. of those admitted to Black Notley. The mean duration in the Edinburgh series was 7·3 years, that in the E.R.C. Aspirin-Cortisone Trial 7·1 years, and that in the Massachusetts General Hospital series 5·1 years. The duration of disease was longer, therefore, in the Black Notley patients, than in the other groups.

(*d*) *Age at Onset of Disease* (Table I).—The Black Notley patients showed no important differences from the other groups, the mean age being 42·3 years.

(*e*) *Course of Disease before Admission.*—In view of the suggestion by Duthie and others (1955) that there may be, at least in the early cases, some connexion between the course of the disease before admission and the subsequent prognosis, we classified our patients in the same manner as Duthie and his colleagues into three groups (Fig. 3):

(1) Those whose disease had been rapidly progressive since an acute onset;

(2) Those in whom the course had been characterized by exacerbations and remissions of variable duration;

(3) Those with insidious onset and slowly progressive disease.

It will be seen that in nearly two-thirds of the Black Notley cases the disease took a progressive course compared with 40 per cent. of the Edinburgh cases and 40 per cent. also of our London Hospital in-patients. It is generally thought that it is the slowly progressive natural history which carries the worst prognosis, and if this is so then the Black Notley patients represent, as a group, those with the worst prognosis.

(*f*) *Functional Capacity on Admission.*—All patients were assessed for functional capacity on admission on the same basis as that in general use: Grade I representing fitness for all normal activities, Grade II some restriction but complete independence, Grade III some degree of dependence, and Grade IV complete dependence (Fig. 4, overleaf).

All the Black Notley cases were equally distributed between Functional Capacities III and IV. Only nine of the 62 cases (14 per cent.) of the London Hospital in-patient series were in Functional Capacity IV, and 24 (39 per cent.) were in Functional Capacity I or II, a distribution very similar to the Edinburgh series. In the Empire Rheumatism Council out-patient series, no less than 70 per cent. were in Functional Capacity I or II. The present series, therefore, was considerably worse in terms of functional capacity than the other series used for comparison.

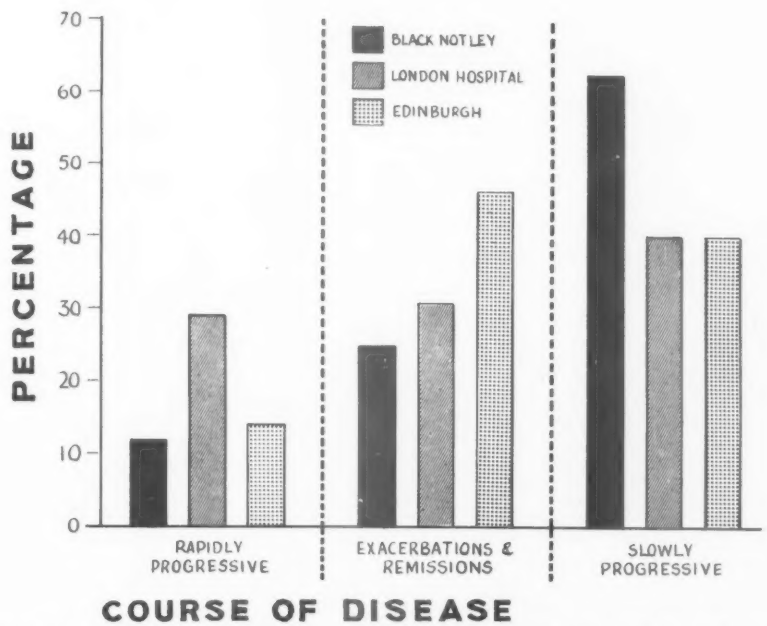

Fig. 3.—Course of disease before admission to hospital in three series of patients (London, Edinburgh, and Black Notley).

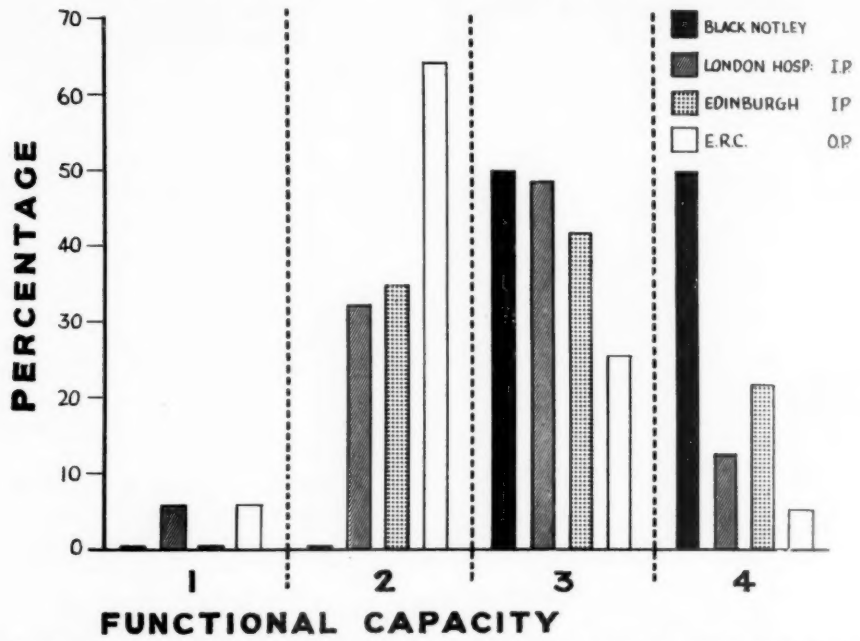

Fig. 4.—Functional capacity on admission to hospital in four series of patients (London, Edinburgh, Black Notley, and E.R.C.).

(*g*) *Disease Activity on Admission.*—This was also assessed by the criteria of Duthie and others (1955), Grade 1 representing very active disease, Grade 2 moderately active disease, and Grade 3 inactive disease (Fig. 5). In terms of disease activity the Black Notley material does not differ significantly from the other series.

In summary, therefore, the patients selected for admission to Black Notley represented the more severe group of rheumatoid arthritics when considered in terms of disease duration, previous course of the disease, and functional capacity, whilst the disease activity was similar to that in other groups admitted to hospital in London and Edinburgh.

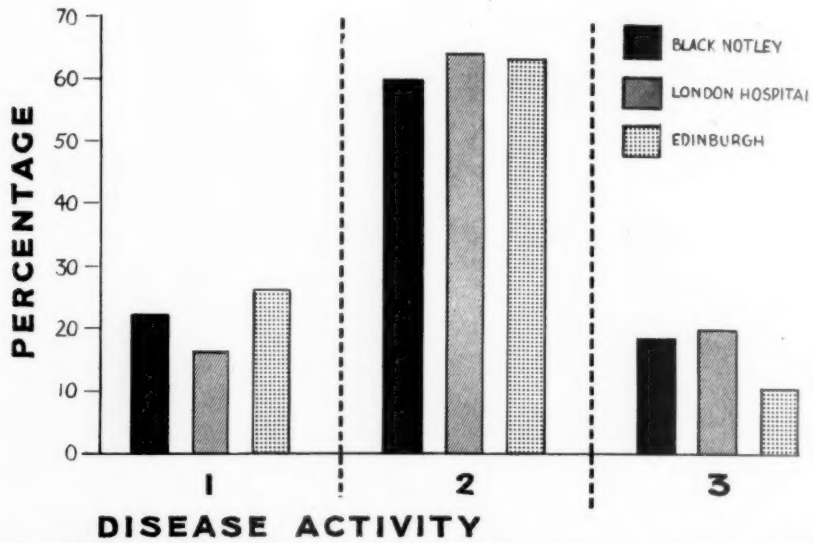

Fig. 5.—Disease activity on admission to hospital in three series of patients (London, Edinburgh, and Black Notley).

Duration of Hospitalization

Two patients discharged themselves after 1 and 2 months' stay at Black Notley. The remaining 38 stayed for an average of 6 months and 2 weeks; the range was from just under 4 months to 20 months, the largest number staying between 5 and 8 months (60 per cent.). The average duration of hospitalization of Duthie's cases was 9 to 10 weeks (range 2 weeks to 9 months).

Results

(*a*) *Functional Capacity*.—Fig. 6 shows a comparison between the functional capacity on admission, discharge, and follow-up. On discharge there was a distinct improvement in the Black Notley cases, 70 per cent. of which are now in Grade III, leaving only 22·5 per cent. in Grade IV. These nine cases represent the hard core of severely and permanently crippled arthritics and comprise about one-quarter of the whole. Three cases have moved up to Grade II (7·5 per cent.); this improvement is highly significant ($P<0·01$). On follow-up two of our patients (5 per cent.) were found to have moved up to Grade I, and a further five had improved to Grade II. Duthie's patients behaved in much the same way, in that on the whole they continued to improve after discharge with a slight tendency to slip back to Grade IV.

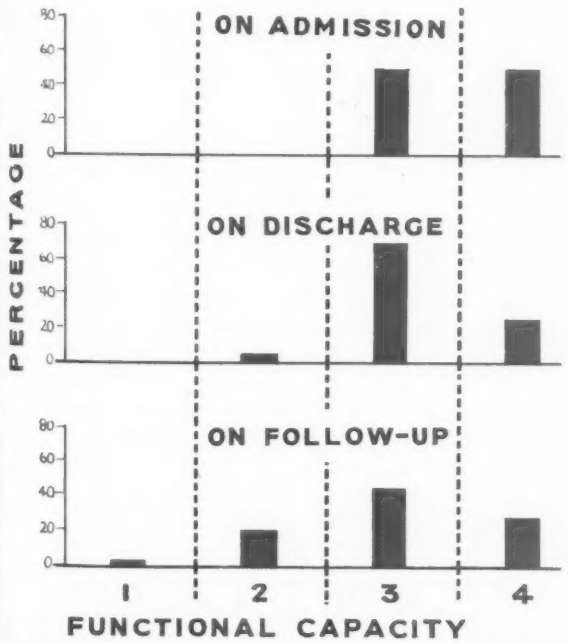

Fig. 6.—Functional capacity on admission to Black Notley, on discharge, and on follow-up.

(*b*) *Disease Activity* (Fig. 7).—There was a moderate degree of improvement in disease activity between admission and discharge. Although this is not as striking as that seen in functional capacity, it does just reach significance at the 5 per cent. level. Follow-up figures showed little change.

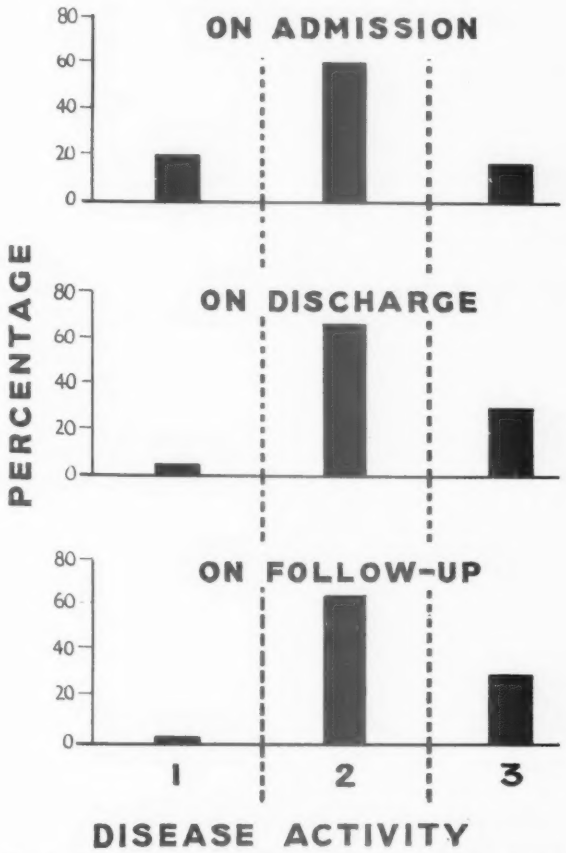

Fig. 7.—Disease activity on admission to Black Notley, on discharge, and on follow-up.

(*c*) *Effect on Erythrocyte Sedimentation Rate and Haemoglobin Percentages* (Table II).—A moderate fall in the mean erythrocyte sedimentation rate

TABLE II

MEAN SEDIMENTATION RATE AND HAEMOGLOBIN LEVELS ON ADMISSION, DISCHARGE, AND FOLLOW-UP

Time of Estimation	Mean Erythrocyte Sedimentation Rate (mm./hr)	Mean Haemoglobin (per cent.)
On Admission	50·4	69
On Discharge	37·5	79
On Follow-up	39	79

occurred, and a rise in haemoglobin of 10 per cent. was also observed. Both these changes are significant ($P<0{\cdot}01$). Little change occurred on follow-up.

Relationship of Functional Capacity on Admission to Functional Capacity on Discharge (Table III).—Of all those initially in Grade III only three out of twenty went up to Grade II, whilst thirteen out of twenty initially in Grade IV moved up to Grade III. It would thus appear that the severely incapacitated case does well on prolonged hospitalization, but that it is difficult to make the jump from Grade III to Grade II.

Follow-up figures show that nine patients moved from Grade III on discharge to Grade II, one from Grade III to Grade I, and one from Grade II to Grade I.

Only one patient moved down from Grade III on discharge to Grade IV on follow-up.

TABLE III

RELATIONSHIP OF FUNCTIONAL CAPACITY ON DISCHARGE TO GRADE OF FUNCTIONAL CAPACITY ON ADMISSION

Grade of Functional Capacity on Admission	Functional Capacity on Discharge		
	Improved	Same	Worse
I		0	0
II	0	0	0
III	3	14	1
IV	13	7	
Total No. of Cases	16	21	1

Relationship of Duration of Disease to Improvement in Functional Capacity on Discharge (Table IV).—Patients in whom the disease is of short duration are more likely to improve their functional capacity on this regime, and as disease duration increases the likelihood that this will occur diminishes progressively.

TABLE IV

RELATIONSHIP OF FUNCTIONAL CAPACITY ON DISCHARGE TO DURATION OF DISEASE ON ADMISSION

Duration of Disease (yrs)	Functional Capacity on Discharge		
	Improved	Same	Worse
Under 1	3	0	0
1–5	6	6	0
6–10	4	5	0
Over 10	3	10	1
Total No. of Cases	16	21	1

Relationship of Disease Activity on Admission to Improvement in Functional Capacity on Discharge (Table V).—Of those initially in disease activity Grade 1, five out of nine improved their functional capacity, three remained the same, and one discharged herself prematurely. Of those initially in disease activity Grade 2, nine out of 25 improved their functional capacity, fifteen remained the same, and one became worse. Of those initially in disease activity Grade 3, two improved their functional capacity, three remained the same, and one discharged herself.

TABLE V

RELATIONSHIP OF FUNCTIONAL CAPACITY ON DISCHARGE TO GRADE OF DISEASE ACTIVITY ON ADMISSION

Grade of Disease Activity on Admission	Functional Capacity on Discharge		
	Improved	Same	Worse
1	5	3	0
2	9	15	1
3	2	3	0
Total No. of Cases	16	21	1

These figures suggest that a high grade of disease activity on admission is more likely to be followed by improvement in functional capacity, a finding with which Duthie and others (1955) agree. On follow-up it is noticeable that those who slipped back a grade in functional capacity were those whose disease activity was persistently Grade 2 or 3.

Synovectomy.—Thirteen patients (32 per cent.) had synovectomies carried out by Mr. M. C. Wilkinson during their stay at Black Notley. The joints operated on included ten knees, three wrists, two elbows, and one ankle. Of these thirteen, five were of functional capacity Grade III on admission and the remaining eight were in Grade IV. On discharge only two were in Grade IV, ten in Grade III, and one in Grade II. At follow-up only one had reverted to Grade IV. Synovectomy did not appear to have any significant effect on the disease activity of those patients in whom the operation was performed.

Discussion

Duthie and others (1955), and Duthie, Brown, Knox, and Thompson (1957), whose material we have largely used for comparison, have clearly shown that, in a large group of patients with rheumatoid arthritis with sufficiently severe disease to

warrant admission to hospital, satisfactory results can often be obtained by rest in bed combined with splinting, physiotherapy, and simple analgesics. Some two-thirds of their patients were eventually able to lead a useful and independent life. However, one-third of their group had a functional capacity only one grade below normal on admission and, as they point out, a high functional capacity on admission carries a good prognosis as regards functional capacity on discharge. All our patients, by contrast, were in functional capacity Grade III and IV, and had also had a longer disease duration than the Edinburgh group.

The effect of prolonged hospitalization of the order of 6 months on rheumatoid arthritis does not appear to have been reported before. We consider that our preliminary data suggests that this course is worth pursuing. Our finding that functional capacity does improve with hospitalization *alone* without making use of modern rehabilitation techniques, whilst disease activity appears to be less favourably influenced, suggests that a different emphasis should perhaps be placed on the "sanatorium regime" *versus* rehabilitation. It seems clear that disease activity does not improve strikingly with even prolonged sanatorium treatment, a finding which lends no support to any suggestion that it is simply the natural history of the disease which is being recorded. On the other hand, perhaps more important, it seems that, even without rehabilitation, functional capacity is partially dissociated from disease activity. We suggest, therefore, that much greater concentration on rehabilitation is desirable, and might well produce better results than those reported here. Our preliminary view is that the use of beds in sanatoria is justified for the special group of rheumatoid arthritics studied here and might well be expanded. This will require the provision of close, specialized, medical supervision, so that use may be made of steroid or other drug therapy where indicated, which may be fitted in to the whole problem presented by these severe cases.

Finally, public recognition of the need to accept prolonged hospitalization may have to be fostered. This would make it possible to provide treatment for the type of case which the general hospital for various reasons cannot handle.

Summary

For the past 4 years, ten beds for female patients which were previously used for the treatment of tuberculosis at Black Notley Sanatorium have been made available to us. During this time forty patients with severe rheumatoid arthritis were admitted for an average stay of 6½ months. They were treated on standard sanatorium lines with prolonged rest in bed as much out of doors as possible and with suitable splinting. All other treatment was much restricted. This group of patients had a higher duration of disease than those admitted to our beds in the London Hospital during the same period (an average of 9·4 years compared with 7·5). A comparison of the Black Notley group of patients with other comparable groups shows that they represented a more severely affected group as measured by functional capacity and course of disease before admission, although there were no significant differences in the degree of disease activity.

At the time of discharge there was a significant improvement in the Black Notley cases in functional capacity, the proportion only partially disabled increasing from 50 to 68 per cent. and the proportion completely incapacitated decreasing from 50 to 24 per cent. At follow-up (average time 17 months), further improvement in functional capacity was observed. Improvement in disease activity also took place, although this improvement was less than that in functional capacity. Severe incapacity appeared to be no contraindication to admission to the sanatorium regime, but the functional capacity of patients with a short duration of disease improved more than that of those with a long duration of disease.

This preliminary data suggests that sanatorium treatment of rheumatoid arthritis is worth pursuing, but that much greater emphasis should be placed on adequate rehabilitation procedures.

We gratefully record our appreciation to Mr. M. C. Wilkinson and to Dr. W. S. Tegner for allowing us to report patients under their care.

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DISCUSSION

MR. M. C. WILKINSON (*Black Notley*) said that he was pleased that Black Notley had been selected for this experiment. He had noticed that, in the past, patients with rheumatoid arthritis misdiagnosed as tuberculosis had seemed to do as well as the tuberculous cases on sanatorium treatment. Before antibiotics had been

available, the value of open-air therapy for tuberculosis had been acknowledged. He believed that there were certain similarities between rheumatoid arthritis and tuberculosis, and sometimes the two occurred in the same person. He made a plea for rather earlier operative treatment of rheumatoid joints—particularly for limited debridements.

PROF. KELLGREN said that information about these severe cases was useful, but that this was the type of case one would expect to benefit least from rest in bed. A controlled trial of the effect of conservative treatment in milder cases was desirable.

DR. WENLEY agreed that the crucial question was the comparison between in-patient rest in bed and out-patient care without rest in bed in the early cases. It would be difficult to work such a trial, but it should be possible now that it had been shown that even patients with chronic deforming disease could respond to such treatment.

DR. J. J. R. DUTHIE (*Edinburgh*) said that in his hospital they were taking the matter one stage further in terms of rest. They were putting all affected joints into splints, and could at least say that rheumatoid joints did not become ankylosed when immobilized for a month. Information about this sort of in-patient treatment was essential in view of the increasing availability of sanatorium beds which might be used for the treatment of rheumatoid arthritis.

MR. OSMOND-CLARKE (*London*) reminded members that rest for any acute joint had been advocated for many years, at least since the days of Hilton and H. O. Thomas. This form of treatment had been in existence at the Robert Jones and Agnes Hunt Hospital at Oswestry since the early 20th century and had been used too in Edinburgh, Black Notley, and many other centres. He hoped that members would not be too eager to accept Mr. Wilkinson's plea for debridement type of surgery in rheumatoid arthritis; clearly there was a place in the doubtful joint for early biopsy.

PROF. KELLGREN thought that in the past they had been misled about the effect of plaster splinting by its misapplication in patients with ankylosing spondylitis. In this disease splinting had very bad results indeed, and this had suggested that splinting in general was bad.

PROF. E. G. L. BYWATERS (*Taplow*) said that patients who came to hospital came at a time when they were in a relapse, so that almost any form of treatment was likely to be followed, in the majority of cases, by some improvement. What was needed was a comparison with a control series. He thought that it was fashionable to advocate rest in bed for rheumatoid arthritis, but this could be carried so far that the patient continued to be carried.

DR. H. F. WEST (*Sheffield*) hoped that trials of prolonged rest in bed would not be carried out on patients who had young children at home.

In answer to a member who asked how long patients were kept in bed, Dr. Wenley said that they were given from 4 to 6 weeks of complete rest.

Traitement de l'arthrite rhumatismale par un régime de sanatorium. "L'expérience de Black Notley"

RÉSUMÉ

Pendant les dernières 4 années dix lits pour des femmes, antérieurement destinés au traitement de la tuberculose au sanatorium de Black Notley, se trouvaient à notre disposition. Pendant ce temps quarante malades atteintes d'arthrite rhumatismale sévère y avaient été admises et ont séjourné pendant 6½ mois en moyenne. Elles étaient soumises au régime ordinaire de sanatorium, avec repos prolongé au lit, en plein air autant que possible, et avec attelles appropriées. Tout autre traitement était très réduit. Chez ces malades la durée antérieure de la maladie était plus grande que chez des malades admises dans nos salles à *London Hospital* à la même période (9,4 ans comparé à 7,5 ans en moyenne). Une comparaison du groupe des malades de Black Notley aux autres groupes similaires montre que celui-là était plus sévèrement atteint en ce qui concerne la capacité fonctionnelle et l'évolution de la maladie avant l'hospitalisation, bien qu'il n'y avait pas de différence appréciable en ce qui concerne le degré d'activité de la maladie.

Au moment du renvoi de Black Notley on a noté une amélioration fonctionnelle appréciable; le pourcentage des invalides partielles était augmenté de 50% à 68% et le pourcentage des invalides totales diminué de 50% à 24%. A la revue (au bout de 17 mois en moyenne), l'amélioration fonctionnelle était augmentée. On a noté aussi une amélioration de l'activité morbide, bien qu'elle fusse moins accentuée que celle de la capacité fonctionnelle. Une incapacité sévère ne semblait pas constituer une contre-indication à l'admission au régime de sanatorium, toutefois, la capacité fonctionnelle des malades depuis peu de temps s'améliorait plus.

Ces données préliminaires suggèrent que le traitement de sanatorium de l'arthrite rhumatismale vaut bien la peine, on doit cependant insister beaucoup plus sur des procédés de rehabilitation appropriés.

Tratamiento de la artritis reumatoide con un régimen de sanatorio. "El experimento de Black Notley"

SUMARIO

Durante los últimos cuatro años diez camas para mujeres, anteriormente destinadas al tratamiento de la tuberculosis en el sanatorio de Black Notley, fueron puestas a nuestra disposición. Durante este tiempo 40 enfermas con artritis reumatoide severa se admitieron y quedaron durante un promedio de 6½ meses, siendo sometidas a un régimen regular de sanatorio, con reposo en cama y al aire libre cuando posible y con soporte ortopédico apropiado. Otras formas de tratamiento fueron muy reducidas. En estas enfermas la duración anterior de la enfermedad fué mayor que en enfermas similares en nuestro servicio en el *London Hospital* durante el mismo período (9,4 años comparados con 7,5 años, en promedio). En comparación con otros grupos similares, el grupo de enfermas de Black Notley fué más gravemente afecto en su capacidad funcional y en la evolución de la enfermedad antes de la hospitalización, aunque no hubo diferencia apreciable en el grado de la actividad mórbida.

Al tiempo de la salida de Black Notley, se notó una mejoría apreciable de la capacidad funcional; el por ciento de las parcialmente incapacitadas fué aumentado de un 50% a un 68%, mientras el por ciento de las totalmente incapacitadas disminuyó de un 50% a un

24%. A la revista (en promedio después de 17 meses) la mejoría funcional fué aumentada. Se notó también una mejoría en la actividad mórbida, aunque menos acentuada que en la capacidad funcional. Una incapacidad grave no pareció contra-indicar la admisión al régimen de sanatorio, pero en una enfermedad de poca duración la capacidad funcional mejoraba más que cuando la enfermedad había durado mucho tiempo.

Estos datos preliminares sugieren que el tratamiento de sanatorio de la artritis reumatoide vale la pena, se debe, sin embargo, insistir mucho más sobre métodos de rehabilitación apropiados.

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CORTICOTROPHIN (ACTH) IN RHEUMATOID ARTHRITIS

BY

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In the original investigation reported by Hench, Kendall, Slocumb, and Polley (1949), both cortisone and corticotrophin were found to suppress the inflammatory element of rheumatoid arthritis. Since then a large number of reports have been published on the effects of oral steroids in this disease, but only a few have described further experience with corticotrophin.

Corticotrophin has the disadvantage that it must be given by injection, and this is probably the main deterrent to its use in treatment. A further impediment may have been the consideration that the indirect action of corticotrophin through adrenal stimulation made the control of long-term corticosteroid therapy in rheumatoid arthritis and other chronic diseases unduly complicated. This indirect action may, however, be turned to advantage, since it is possible, by estimating the urinary steroid excretion, to measure the degree of adrenal stimulation produced and adjust the dose accordingly.

There appears to be one definite merit in corticotrophin as opposed to oral corticosteroid therapy. Symptoms of adrenal insufficiency (including fatigue, hypotension, dizziness, and muscular weakness) occur not uncommonly when oral steroids are withdrawn, after even a relatively short period of treatment. Although these symptoms are usually the result of an abrupt cessation, they may occur even with gradual withdrawal of the steroid, and whilst they are generally unpleasant rather than dangerous, severe adrenal insufficiency does occasionally occur. On the other hand, in our experience, even abrupt cessation of corticotrophin after prolonged administration is not followed by this type of adverse reaction.

Present Investigations

During the last 8 years we have studied patients with severe rheumatoid arthritis during the administration of either oral steroids or corticotrophin as a long-term regime. The indication for the use of a corticosteroid or corticotrophin was severe active disease in which progress had not been checked by rest, salicylates, and, in most cases, gold. These patients were affected to the extent that they would have been unable to continue their occupations unless the disease could be suppressed, and most of them had already had to stop working.

Material.—The group treated with oral steroids comprises 104 cases and is being used only for comparison of the side-effects. The group treated with corticotrophin comprises 78 cases; the length of administration is shown in Table I.

TABLE I

DURATION OF TREATMENT OF 78 PATIENTS

Duration of Treatment (yrs)	7	6	5	4	3	2	1	6-12 mths	Total
	1	2	5	3	4	19	21	23	78

Method.—In 58 of these cases regular estimations of urinary steroid excretion were carried out to try to correlate the level of adrenal stimulation with the degree of suppression of the arthritis and with the occurrence of side-effects. Norymberski's method for estimating the excretion of 17-hydroxy-corticosteroids (17(OH)CS) was used (Appleby, Gibson, Norymberski, and Stubbs, 1955). While in hospital for the start of treatment, patients were taught in the biochemical laboratory to measure a 24-hr specimen and when they left hospital they were lent a litre-measuring cylinder and a number of 1-oz. (31-ml.) containers with wooden cases which could be sent through the post. As they were nearly all working, they collected their specimens at the week-end, and used small plastic bottles for urine collection when they went out during the day. An aliquot of the well-mixed specimen with a note of the 24-hr volume was sent by post to the laboratory each week. The accuracy of the 24-hr urine collection was checked by creatinine determinations.

We did not attempt to maintain any given level of adrenal stimulation, but regulated the dose of

corticotrophin primarily by the clinical response whilst observing 17(OH)CS excretion. We hoped thus to avoid over-stimulation and minimize side-effects.

The adreno-cortical response varies during treatment, and it is therefore important that the urinary steroid excretion should be checked at intervals. We do not know the reason for this variation, whether it is the activity of the disease, or some change in the cortex, but certain patterns of response have become familiar, and are discussed below.

Results of Treatment

In view of the difficulty of assessing the value of therapy in rheumatoid arthritis, especially over short periods of time without careful controls, this report is confined to the clinical response of a subgroup of forty cases in whom estimations of corticosteroid excretion and clinical assessments were carried out regularly from the start of treatment and were followed up for at least 2 years. This was the period of the Medical Research Council/Nuffield Cortisone-Aspirin Trial (1955), which, in the absence of a true control series, is here used for comparison. It should be noted, however, that the M.R.C./Nuffield trial included only early cases (3 to 9 months' duration) in which the prognosis would be expected to be more favourable than in our group.

In thirteen of these forty cases, corticotrophin was discontinued before the end of the 2 years because the patients' response was unsatisfactory: in six because of side-effects, and in seven because a satisfactory level of adrenal stimulation could be maintained only with uneconomically large doses of corticotrophin. Since in these cases oral corticosteroid therapy was substituted, they have been excluded from the results given below.

In six of the remaining 27 cases, it was possible to withdraw corticotrophin before the end of 2 years because it was no longer required; the clinical assessments were continued and are included in the results. The other 21 cases were still receiving corticotrophin at the end of the 2 years under review. These figures are summarized in Table II.

Clinical Assessments

In this study, clinical assessment was based on strength of grip and joint tenderness. The erythrocyte sedimentation rate has also been used as a measure of progress. Ability to carry out everyday actions, such as getting in and out of a bath unaided, has proved useful in assessing the progress of individual cases but cannot be summarized in the group results.

(*a*) *Strength of Grip.*—In most cases of rheumatoid arthritis, change in the strength of grip reflects closely the activity of the disease and forms the best single guide to progress. Strength of grip was measured by means of a sphygmomanometer cuff enclosed in a bag 6 in. long and 3 in. wide connected to a standard sphygmomanometer, so that 260 mm. Hg was the maximum recordable reading.

Table III (overleaf) shows the average readings of the sum of the grip of both hands in the 27 patients who completed the 2-year period of observation, together with the equivalent results in the M.R.C./Nuffield Trial.

Another mode of presentation of the results of tests of strength of grip, which was used in the M.R.C./Nuffield Trial, indicates the proportion of cases who showed given changes in their strength of grip during the 2-year period of study. Our results are compared with those of the M.R.C./Nuffield Trial in Table IV (overleaf).

(*b*) *Joint Tenderness.*—Joint tenderness to firm digital pressure is recorded in three grades, the average of the joints involved being taken as the index of joint tenderness. The results of the present study are shown in Table V (overleaf).

TABLE II

CASES OBSERVED FOR 2 YEARS
(with 17(OH)CS estimations from start of treatment)

Sex		Men	Women	Total	
Corticotrophin Stopped	Because of side-effects	—	6	6	13
	Because of "resistance"	2	5	7	
	Because of favourable course of disease	2	4	6	27
Still having corticotrophin at end of 2 years		10	11	21	
Total Patients		14	26		40

TABLE III

RESULTS OF TESTS OF STRENGTH OF GRIP

Trial		No. of Cases	Mean Age (yrs)	Mean Duration of Disease (yrs)	Means of Sum of Grip of Both Hands (mm. Hg)		
					At Start	After 1 year	After 2 years
Present Study		27	40·7	4·5	253	457	445
M.R.C./Nuffield (1955)	Cortisone ..	30	45	0·5	272	389	373
	Aspirin	28			227	330	322

TABLE IV

CHANGES IN STRENGTH OF GRIP AFTER 2 YEARS FROM START OF TREATMENT

Hand	Trial		No. of Cases	Change in Strength of Grip (mm. Hg)					
				Improved			None	Deteriorated	
				By 100 mm. Hg or More		By Less than 100 mm Hg		By Less than 100 mm. Hg	By 100 mm. Hg or More
				No.	Per cent.				
Right	Present Study		27	13	48	10	2	1	1
	M.R.C./Nuffield	Cortisone ..	30	7	23	14	1	6	2
		Aspirin	28	4	14	15	3	6	—
Left	Present Study		27	16	59	9	2	—	—
	M.R.C./Nuffield	Cortisone ..	30	11	37	12	1	5	1
		Aspirin	28	7	25	14	1	6	—

TABLE V

RESULTS OF ASSESSMENT OF AVERAGE JOINT TENDERNESS

Trial		No. of Cases	Mean Age (yrs)	Mean Duration of Disease (yrs)	Mean "Average" Joint Tenderness		
					At Start	After 1 Year	After 2 Years
Present Study		27	40·7	4·5	1·35	0·30	0·30
M.R.C./Nuffield	Cortisone	30	45	0·5	1·91	0·74	0·72
	Aspirin	28			1·89	0·76	0·58

TABLE VI

RESULTS OF ERYTHROCYTE SEDIMENTATION RATE ESTIMATIONS (mm./hr)

Trial		No. of Cases	Mean Age (yrs)	Mean Duration of Disease (yrs)	Mean E.S.R. (mm./hr)		
					At Start	After 1 Year	After 2 Years
Present Study (Westergren)		27	40·7	4·5	43	13	18
M.R.C./Nuffield (Wintrobe)	Cortisone ..	30	45	0·5	42	27	29
	Aspirin ..	28			42	35	28

(*c*) *Erythrocyte Sedimentation Rate.*—The means obtained in this study (Westergren) are listed in Table VI with those of the M.R.C./Nuffield Trial (Wintrobe).

Persistence of Response to Corticotrophin

One of the difficulties in long-term treatment with oral steroids is the tendency for the suppression of the arthritis to lessen after a time. Higher dosage is then required, bringing with it an increased risk of severe side-effects. In an attempt to combat this diminishing effect, patients are often changed to one or other of the newer analogues of cortisone, but this again may only succeed for a short time. It appears that the original effectiveness of corticotrophin persists over long periods. Fig. 1 shows the means of the clinical assessments in the 27 cases who responded satisfactorily over a 2-year period, including six in which the drug was withdrawn without relapse.

Relation of 17(OH)CS Excretion and Clinical Response

The large majority of normal values for 17(OH)CS excretion fall within the range of 5-15 mg./24 hrs (Moxham and Nabarro, 1956; Borth, Linder, and Riondel, 1957). In most cases of severe active rheumatoid arthritis, the excretion is nearer the lower level of these limits (about 5-10 mg./24 hrs). West (1957) has stated that, if the pre-treatment level of steroid excretion is doubled, there will be a measurable clinical response, and our experience agrees with this. Therefore, in some cases, it may not be

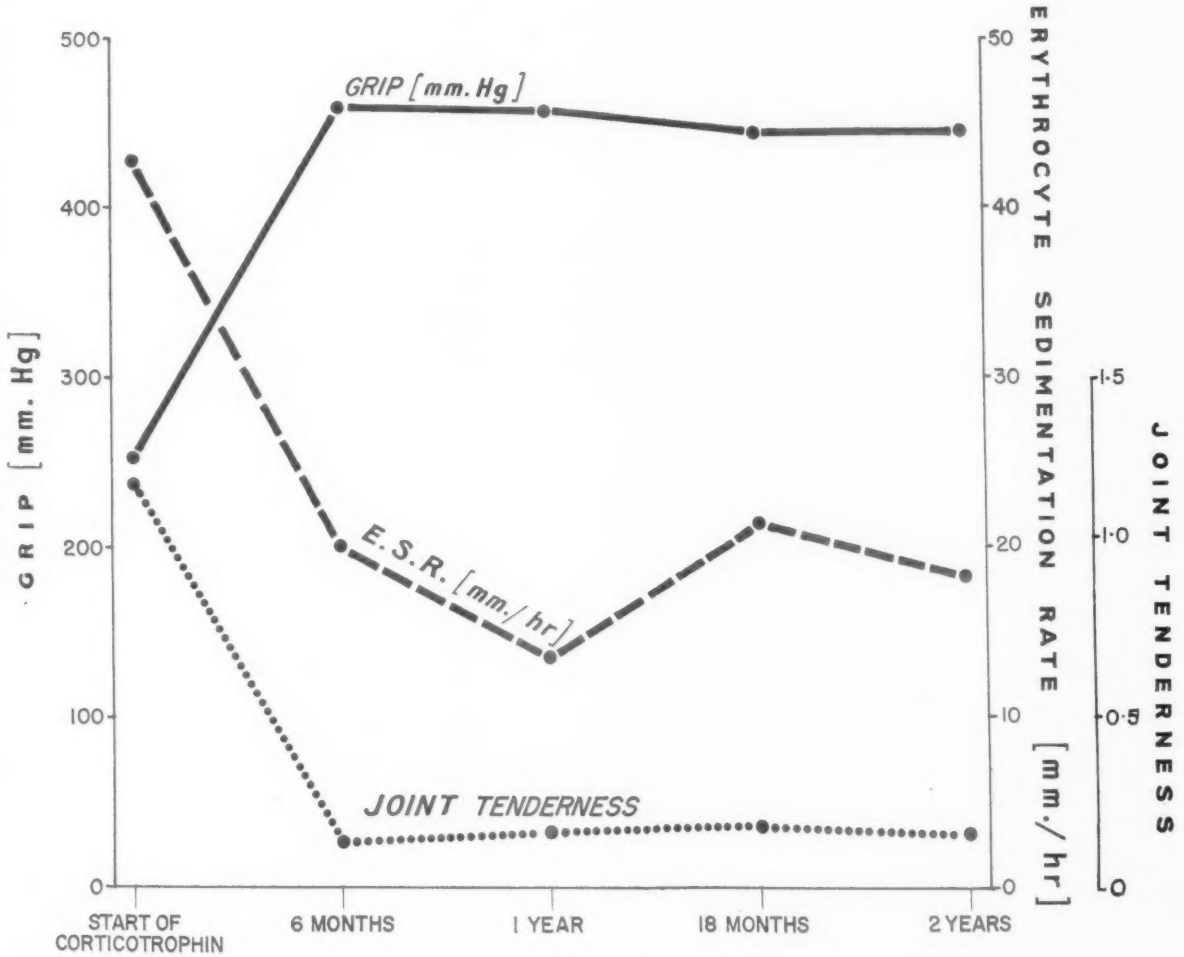

Fig. 1.—Means of clinical assessments in the 27 cases who responded satisfactorily for 2 years (including six "remissions").

necessary to raise the excretion above 15 mg./24 hrs.

In most cases excellent clinical suppression as measured by increase in the strength of grip and abolition of tenderness, can be achieved with a 17(OH)CS excretion of around 20 mg./24 hrs.

Our usual starting dose is 20 units ACTH *per diem*, and as a rule the response is adequate, with a good increase (over 100 per cent.) in the steroid excretion. Occasionally we have had to increase the dose to 30 units *per diem* before obtaining satisfactory adrenal stimulation. After the initial rise there is a marked fall in the steroid level, often to pre-treatment figures, as if the adrenal cortex had become temporarily exhausted. This is followed by a second rise of 17(OH)CS which flattens out. It is at this point that the maintenance dose may have to be adjusted to obtain a satisfactory continuing steroid excretion. Fig. 2 illustrates this point.

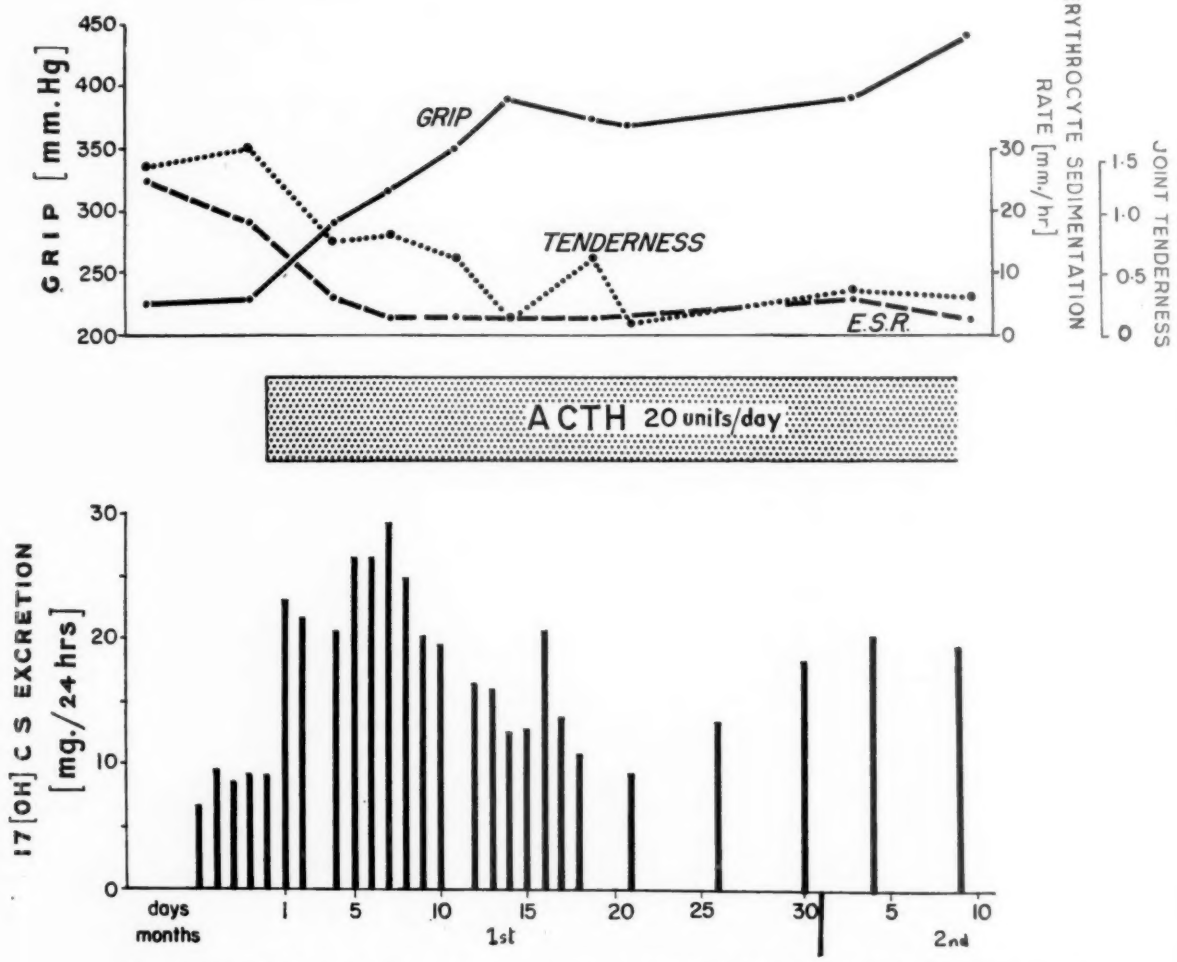

Fig. 2.—Initial rise in steroid excretion with corticotrophin, followed by a fall in excretion and then a secondary rise.

In some patients the steroid excretion remains steady on the same dose for months or years, as in Fig. 3, and no adjustment is necessary.

There are two types of variation which are rare but may occur at any time during treatment. The first is a sudden increase in adrenal response to a dose which has been giving a steady rate of excretion, as illustrated in Fig. 4 (overleaf). This patient, a girl aged 20, produced a sudden unexplained increased steroid excretion in the fourth month of treatment, accompanied by minor side-effects. The dose of corticotrophin had to be reduced rapidly before the 17(OH)CS excretion fell to a safe level. Such a variation will give rise to severe side-effects if it is not recognized early and the dose reduced, and we suspect it to be due to a temporary lessening in the activity of the disease.

Occasionally the steroid excretion tends to diminish after a period on a regular dose of corticotrophin. This trend can usually be reversed by a moderate increase in the dose, but in some cases even doubling the original dose does not produce any rise in steroid excretion: West (1956) has reported this as acquired resistance to the hormone. We have, on occasion, been able to overcome this resistance by further increasing the amount of corticotrophin, but this has required very large doses,

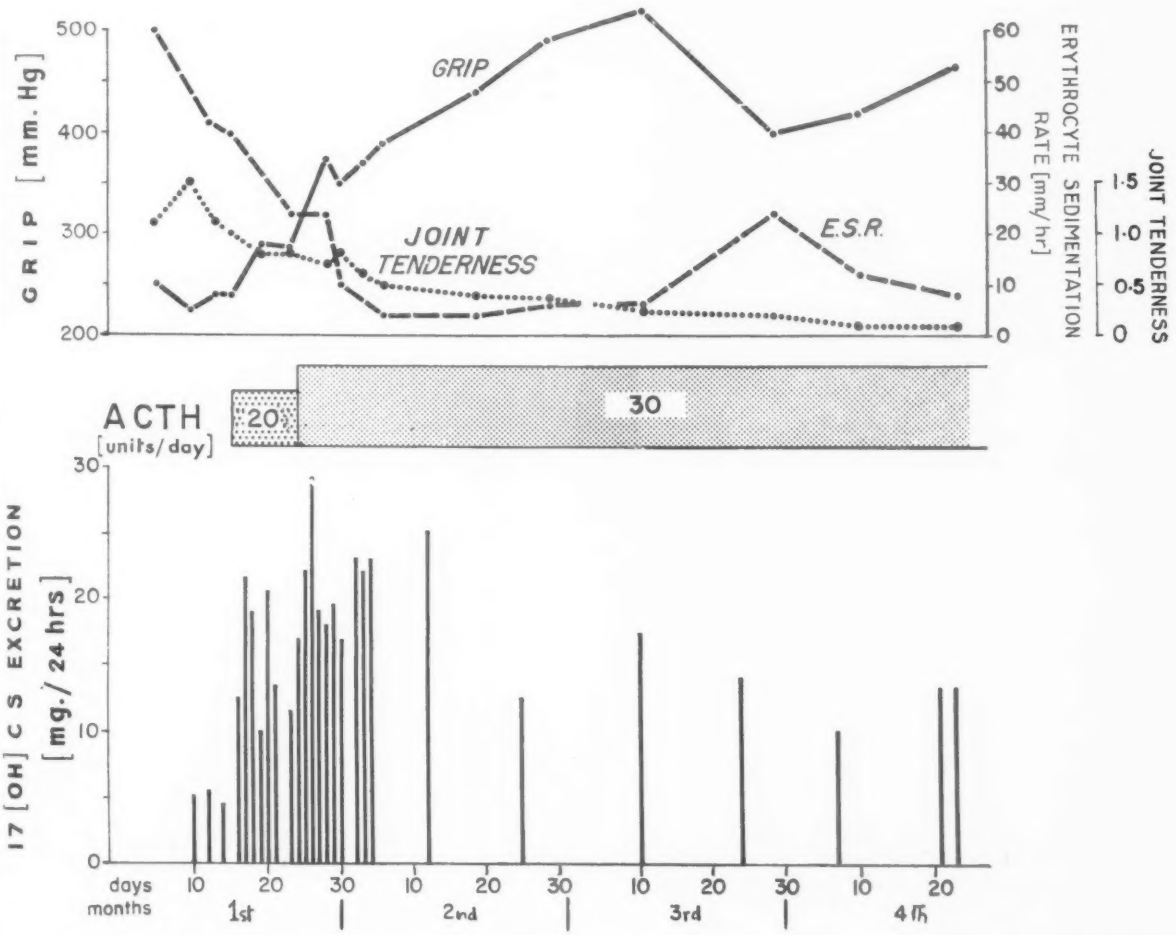

Fig. 3.—Satisfactory degree of clinical suppression accompanied by a steady urinary steroid excretion after the initial adrenal stimulation.

80 units twice daily in one case. Fig. 5 (opposite) illustrates this temporary resistance in a girl aged 17, which was accompanied by clinical relapse during the twelfth month of treatment. It was eventually overcome by doubling the dose for a short period. Once this refractory state has subsided, we have often been able to reduce the dose again quite rapidly to the previous maintenance level. In a few cases it appeared that prolonged high dosage would be necessary to maintain an adequate response and corticotrophin was withdrawn on this account. In the majority of patients, however, little change has been needed over prolonged periods.

Side-Effects

The main difficulty in the long-term treatment of severe rheumatoid arthritis, with either oral steroids or corticotrophin, is the occurrence of severe side-effects. We were anxious to find out if there was any difference between those produced by oral steroids and those produced by corticotrophin in a long-term treatment.

Table VII (overleaf) gives a comparison of two groups observed during the last 8 years, and shows some interesting differences:

(1) Dyspepsia and peptic ulceration are much

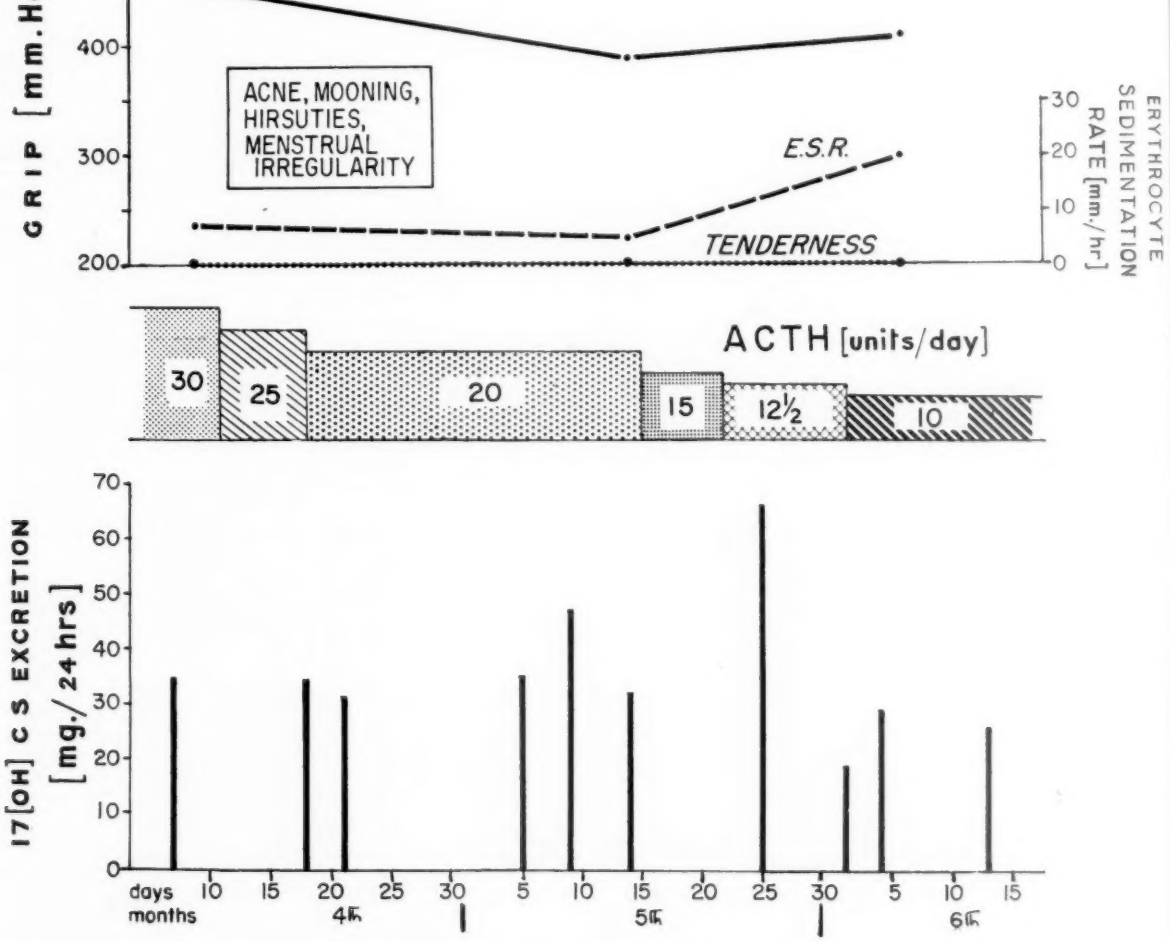

Fig. 4.—Increase in steroid excretion at the fourth month, accompanied by minor side-effects, only corrected by drastic dose reduction.

more common with an oral hormone, which lends support to the theory that this side-effect is due to the local action on the gastric mucosa.

(2) As would be expected, the pituitary hormone is more likely to cause skin trouble such as acne and pigmentation. With corticotrophin acne may be severe, covering the face, chest, and back, and particularly in young women it has been serious enough on a few occasions to necessitate withdrawal or change of the hormone. Pigmentation with corticotrophin has not been a problem and has merely consisted in retention during most of the winter months of sunburn gained in the summer.

(3) Hypertension is more common with corticotrophin. This has been severe enough to cause us to withdraw or change the drug in only six cases.

Correlation of Side-Effects with Level of Adrenal Stimulation

During the last 4 years we have been able to correlate in 58 patients the degree of adrenal stimulation with the occurrence of side-effects.

Hypertension.—There is disagreement whether or not hypotension constitutes a clinical feature of rheumatoid arthritis. Whereas the Empire Rheumatism Council Report (Lewis-Faning, 1950) and Short, Bauer, and

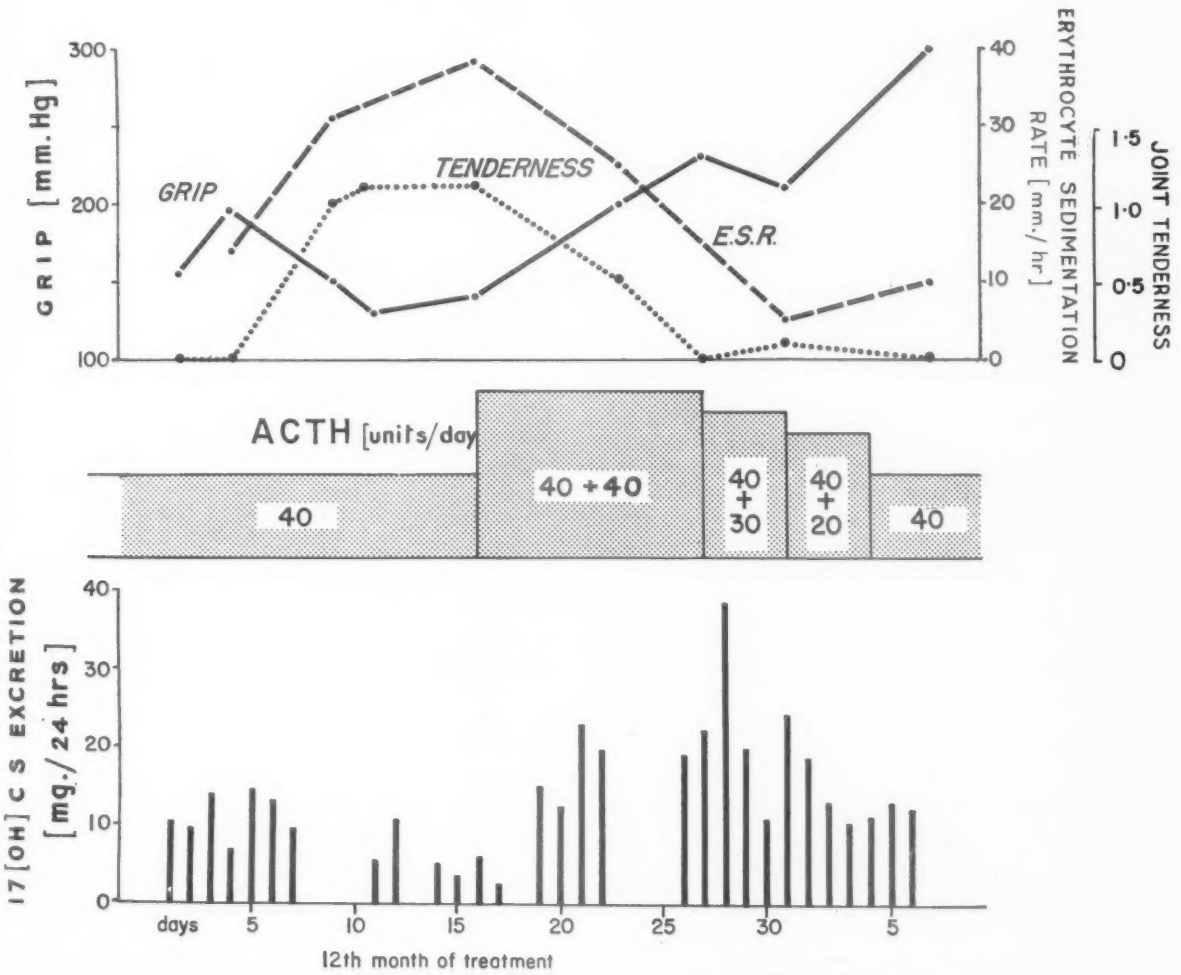

Fig. 5.—Temporary resistance developing in the 12th month of treatment accompanied by clinical relapse. This was overcome by doubling the dose for a short time.

TABLE VII

INCIDENCE OF SIDE-EFFECTS

Therapy		Oral Steroids 104		Corticotrophin 78	
No. of Cases		No.	Per cent.	No.	Per cent.
Side-Effects	Weight Increase	29	27·9	24	30·7
	Moon Facies	54	51·9	42	53·8
	Oedema	34	32·7	23	29·4
	Dyspepsia	49	47·1	12	15·3
	Peptic Ulceration (or Erosion)	12	11·5	2	2·5
	Glycosuria	5	4·8	10	12·8
	Acne	7	6·7	25	32·0
	Hirsuties	20	19·2	17	21·7
	Pigmentation	1	0·96	17	21·7
	Chemosis	3	2·9	6	7·6
	Menstrual Irregularity	11/76	14·3	13/50	26·0
	Hypertension	18	17·3	26	33·3
	Osteoporosis	6	5·8	4	5·1
	Mental Disturbance	2	1·9	3	3·8

Reynolds (1957) were unable to show this, Turner and Lansbury (1954) found a low blood pressure in 320 patients, and in the small group of severe cases reported here it has been quite evident.

All patients have shown some rise of blood pressure when the 17(OH)CS excretion has risen significantly above the normal range. When the excretion has been between 25 and 35 mg./24 hrs, about 15 per cent. of patients have shown a rise in the diastolic pressure to 100 mm. Hg, and when the excretion has exceeded 40 mg./24 hrs, the proportion has risen to about 45 per cent. As a rule these rises in blood pressure are transient and closely parallel the corticosteroid excretion. We have not seen chronic hypertension arise in this way, but, in a few cases, when a high corticosteroid excretion has been maintained for 2 to 3 weeks, the hypertension has persisted after a reduction in dose of corticotrophin has brought the 17(OH)CS down to a lower level, and the blood pressure has then fallen only gradually over a period of weeks or months.

Glycosuria.—As with the blood pressure responses, some patients have shown transient glycosuria when corticosteroid excretion has been high. One patient developed a true "steroid diabetes"; this was a man who showed evidence of marked adrenal stimulation when he was given what proved to be a very potent batch of corticotrophin. Despite rapid reduction of the dose, his 17(OH)CS excretion rose from 40 to 105 mg./24 hrs over a period of 5 weeks. It then fell to about 80 mg., but after a further 3 weeks he developed glycosuria, with polyuria and thirst, and a glucose-tolerance test showed a diabetic type of curve; corticotrophin was withdrawn, and with the fall in 17(OH)CS excretion the glucose tolerance gradually reverted to normal, although there was a significant time-lag. Characteristically, at no time was ketonuria detected.

Fluid Retention and Weight Increase.—All patients have put on some weight while having corticotrophin, but many of them were underweight when treatment was started, and we have taken an increase of 7 lb. (3·2 kg.) or more above their normal weight as being excessive. Improvement in appetite almost always follows effective corticotrophin administration, and such patients have to be warned to check their weight. The majority are able to maintain a normal weight without any drastic dietetic restriction, but in about 20 per cent. strict measures are necessary and on the whole it is this group which shows a tendency to fluid retention. These side-effects appear to be due to individual susceptibility rather than adrenal over-stimulation, and frequently become apparent when the 17(OH)CS excretion rises above 15 mg./24 hrs.

Androgenic Side-Effects.—Acne, hirsuties, and menstrual disturbances were quite common in the younger women. They were rarely severe and often occurred when the 17(OH)CS was raised only slightly above the normal range, that is to 15-25 mg./24 hrs. There appeared to be an individual susceptibility in this respect and as a rule androgenic side-effects were not apparent until the patient had received an effective dose of corticotrophin for at least 3 weeks.

It appears, after studying the correlation between side-effects and the level of adrenal stimulation, that the severe disturbances due to overstimulation occur

when the level of 17(OH)CS excretion rises above 30 mg./24 hrs. These side-effects take some weeks to appear and are reversible, though there may be a considerable time-lag between the lowering of the dose and their consequent disappearance.

Discussion

After 8 years' experience, it is clear that a daily self-administered injection of corticotrophin is a practical long-term method of suppressing the activity of severe rheumatoid arthritis. The majority of the patients who were crippled before this treatment have returned to, and remained at, their occupations, and some 46,000 injections have been given without local complications. Suppression of the arthritis can be maintained and the effect of adrenal stimulation does not become less over long periods.

In an earlier report (Savage, Davis, Chapman, Popert, Robertson, and Copeman, 1957), we pointed out the variability of different batches of the drug, and this has now been corrected by the firms whose material we have used in this series.

The corticotrophin has been withdrawn in 46 of the 78 cases started on a long-term regime. It is interesting to examine the reasons for these withdrawals. In fifteen cases the drug was stopped because the patients were able to lead normal lives without it, requiring only occasional aspirin for pain and stiffness. These patients had previously been incapacitated, but were able to return to work while receiving treatment with corticotrophin. After a few months, as progress was satisfactory, the dose was slowly lowered and in this particular group, as no relapse occurred, the corticotrophin was stopped. During the very active stage of the arthritis corticotrophin had suppressed the disease, and as remission occurred it was found possible to withdraw the drug.

These fifteen cases have been followed up for an average of 3 years, and in only one has there been a significant relapse: a woman aged 25, in whom severe arthritis returned at the fifth month of pregnancy 1 year after the drug had been withdrawn. The previous duration of the arthritis in these fifteen cases varied from 6 months to 13 years. The average length of corticotrophin administration was 9 months, and we could discover no common factor in the pattern of steroid response. In only four of these patients can we consider the disease to be in complete remission. In the remaining eleven there are periods of mild activity and the erythrocyte sedimentation rate remains raised, but salicylates are sufficient to enable them to lead normal lives. In the comparable series of 104 similar patients on oral steroids, we have been able to discontinue the hormone in only two cases.

In the remaining 31 cases corticotrophin was withdrawn either because of side-effects (18 cases) or because of the development of a "resistance" to the drug (13 cases). It might have been possible to overcome the resistance by increasing the dosage, as shown in Fig. 5, but at that time not enough corticotrophin was available for this.

In the 31 cases in which the drug was withdrawn because of side-effects, we found that there was too small a margin between the level of adrenal stimulation needed to achieve worthwhile suppression of the arthritis and that at which side-effects occurred, so that continuing treatment with corticotrophin did not seem practicable. The majority of these patients were transferred to oral steroids.

During this study the value of biochemical control has become evident. With this method of control it is possible to check the degree of adrenal stimulation and, when it appears insufficient or excessive, to adjust the dose accordingly.

During the earlier part of our 8-year study of corticosteroid therapy in severe rheumatoid arthritis, the choice between oral steroids and corticotrophin was determined by supplies. Our preference was for oral steroids when available. It is our current practice, however, to use corticotrophin when long-term steroid treatment is indicated, unless the hands remain too crippled for self-injection to be practicable.

Summary

(1) During the last 8 years, 78 cases of severe rheumatoid arthritis have been studied during the self-administration of corticotrophin by subcutaneous injection.

(2) In 58 cases, regular estimations of urinary 17-hydroxy-corticosteroid levels have been carried out by Norymberski's method.

(3) In 27 cases which responded satisfactorily for over 2 years, the clinical measurements have been compared with the groups of cases of early rheumatoid arthritis reported in the Medical Research Council-Nuffield trial for a similar period.

(4) The majority of these patients have been able to return to their occupations and in fifteen of the 78 the corticotrophin has been withdrawn without relapse of the arthritis.

(5) Side-effects have been correlated with the levels of adrenal stimulation and compared with those in a group of patients receiving oral steroids.

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The corticotrophin used in this study was provided partly by the Ministry of Health and partly by Crookes Laboratories Ltd. of England, and the Armour Laboratories and Wilson Laboratories of the United States of America.

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Corticotrophine (ACTH) dans l'arthrite rhumatismale

RÉSUMÉ

(1) Pendant les dernières 8 années on étudia 78 malades atteints d'arthrite rhumatismale sévère qui s'administraient de la corticotrophine par voie sous-cutanée.

(2) Dans 58 cas on détermina régulièrement les taux des 17-hydroxy-corticostéroïdes par la méthode de Norymberski.

(3) Dans 27 cas qui réagirent d'une manière satisfaisante pendant plus de 2 ans, on compara les données cliniques à celles rapportées par *Medical Research Council-Nuffield*, concernant des groupes de cas d'arthrite rhumatismale précoce traités pendant une période similaire.

(4) La majorité de ces malades purent retourner à leurs métiers et chez 15 sur 78 la corticotrophine fut interrompue sans provoquer une rechute de l'arthrite.

(5) On détermina la corrélation entre les effets secondaires et le degré de la stimulation surrénale et on les compara aux effets secondaires dans un groupe de malades recevant des stéroïdes par voie orale.

Corticotrofina (ACTH) en la artritis reumatoide

SUMARIO

(1) Durante los últimos 8 años se estudiaron 78 enfermos con artritis reumatoide grave que se administraban a sí mismos corticotrofina por vía subcutánea.

(2) En 58 casos se determinó regularmente la cifra de los 17-hidroxi-corticoesteroides por el método de Norymberski.

(3) En 27 casos que respondieron satisfactoriamente durante más de dos años, se compararon los datos clínicos a los contenidos en el informe de las investigaciones de *Medical Research Council-Nuffield* sobre grupos de casos de artritis reumatoide precoz tratados durante un período similar.

(4) La mayoría de estos enfermos pudieron volver a sus ocupaciones y en 15 de los 78 enfermos la administración de corticotrofina fué interrumpida sin provocar una recaída de la artritis.

(5) Se determinó la correlación entre los efectos secindarios y el grado de estimulación suprarrenal, y se compararon estos efectos a los en un grupo de enfermos recibiendo esteroides por vía oral.

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LESIONS OF JOINTS AND TENDON SHEATHS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Joint involvement is recognized clinically as a common feature in systemic lupus erythematosus (SLE). Thus, Ross and Wells (1953), in reviewing the literature, observed that arthralgia or arthritis occurred in 80 per cent. of cases. Harvey, Shulman, Tumulty, Conley, and Schoenrich (1954) and Haserick (1955) recorded incidences of 95 out of 105 and 107 out of 126 cases respectively. Arthritis frequently precedes other symptoms, sometimes by long periods (Dubois, 1953; Harvey and others, 1954; Haserick, 1955). A few authors consider the arthritis to be migratory or transient (Coburn and Moore, 1943), but many comment on the occurrence of changes similar, both clinically and radiographically, to those of rheumatoid arthritis (Slocumb, 1940; Bywaters, 1949; Shearn and Pirofsky, 1952; Friedman, Schwartz, Trubek, and Steinbrocker, 1953; Ross and Wells, 1953; Dubois, 1953; Harvey and others, 1954; Haserick, 1955). Some of these authors regard the rheumatoid type of lesion as unusual (Bywaters, 1949; Haserick, 1955), but others have observed this type of arthritis in over one-quarter of the patients they have studied (Friedman and others, 1953; Ross and Wells, 1953; Dubois, 1953; Harvey and others, 1954). Ankylosis was observed in one patient by Shearn and Pirofsky (1952), and the cases studied by Ross and Wells (1953) included some with rheumatoid lesions of Stage IV (Steinbrocker, Traeger, and Batterman, 1949).

In contrast, little attention has been paid to the histological appearances in the joints. Thus, these lesions are not mentioned in the classical paper by Klemperer, Pollack, and Baehr (1941), although this group of workers describe and illustrate haematoxylin bodies in the synovial tissue in a later article (Klemperer, Gueft, Lee, Leuchtenberger, and Pollister, 1950). Indeed, there appears to be only one article devoted to the joint lesions of SLE (Bennett and Dällenbach, 1951); this describes only the synovial changes and is not readily available outside the United States.

The purpose of the present communication is to describe and illustrate in detail the histological appearances in all components of joints in the disease, and to record, apparently for the first time, the occurrence of tenosynovitis in SLE.

Material and Methods

Tissue was obtained at autopsy from fourteen joints from ten patients, in all of whom the diagnosis was confirmed histologically. Metacarpo-phalangeal and proximal interphalangeal joints were obtained from the right middle finger from three patients and whole sections were cut in an antero-posterior plane. Synovial tissue was taken from the knee (6), ankle (1), or shoulder (1), and flexor tendons and their sheaths from the palm of seven patients. Three blocks were taken from each specimen of synovial tissue and tendon. The blocks were fixed, decalcified when necessary, and embedded in paraffin. Sections from all specimens were stained with haematoxylin and eosin for histological examination and sections from three joints and three tendons were stained by the periodic acid-Schiff, Feulgen, methyl green-pyronin, picro-Mallory, phosphotungstic acid-haematoxylin, toluidin blue, and Prussian blue methods for histochemical study.

Results

Clinical and Radiological Appearances

All but one of the patients had shown clinical evidence of arthritis. In two patients, pain and swelling of joints was the initial symptom, to be followed in a few weeks by other symptoms, including the characteristic rash. In the other patients, evidence of lesions elsewhere had accompanied or preceded the arthritis. The clinical features were pain and swelling involving several joints, most frequently those of the hands and wrists.

Evidence of permanent damage was seen only

once, when well-marked ulnar deviation of the fingers, with subluxation of the metacarpophalangeal joints developed late in the course of the disease (Fig. 1). A radiograph taken a year before death shows marked periarticular osteoporosis and narrowing of the joint spaces in the fingers of both hands.

None of the patients showed clinical evidence of tenosynovitis. Steroid therapy had been used in seven patients.

Morbid Anatomy

Most of the joints showed only minimal changes, such as small effusions and congestion of the synovial tissue. Early pannus was seen on the femoral condyles in two knees and in another knee there was definite acute synovitis. No macroscopic abnormality was detected in the tendon sheaths.

Histology

Joints.—All but one of the fourteen examined showed histological changes, despite the absence of striking macroscopic abnormality.

Synovial Tissue.—Here the most constant and often the most striking feature was the presence of a thick layer of brightly eosinophilic, fibrin-like material on or under the surface (Figs 2 and 3). This material merged with the adjacent synovium

Fig. 1.—Clinical appearance of hands a few months before death, showing bilateral ulnar deviation and subluxation of right metacarpophalangeal joints.

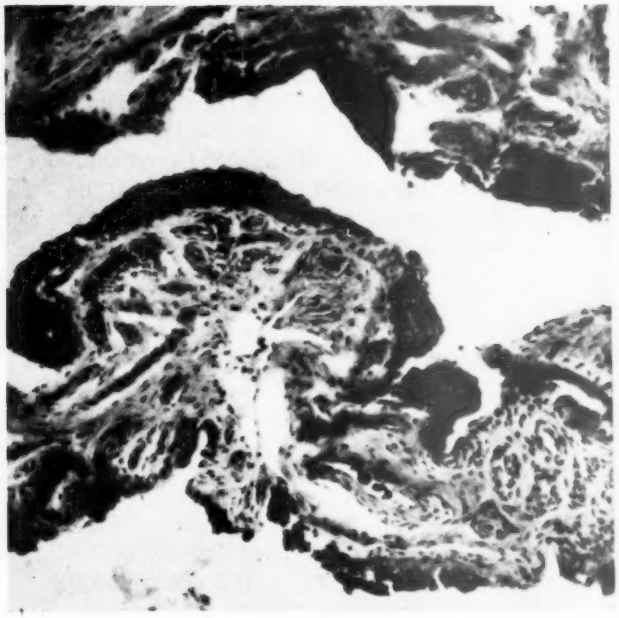


Fig. 2.—Knee (same patient as Fig. 1): portions of two villi with thick layer of fibrin-like material on surface. No inflammation, but some fibrosis in core. Phosphotungstic acid-haematoxylin. × 75.

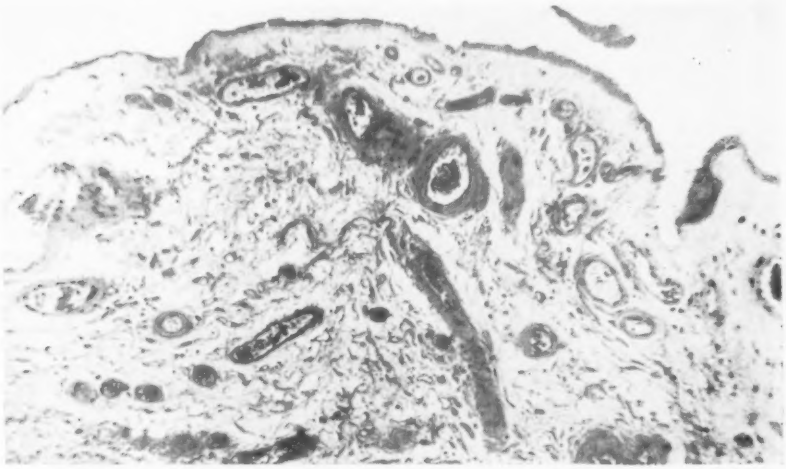


Fig. 3.—Knee: complete loss of synovial lining cells, with layer of fibrin-like material on surface. Oedema of underlying tissue without cellular infiltration. Haematoxylin and eosin. × 55.

and frequently contained pyknotic nuclei. It was seen in eleven joints.

The main change in the synovial cells was a diminution in their number (seven patients).

These two changes were frequently combined so that the eosinophilic material lay directly on the sub-synovial tissue. Sometimes they involved all the tissue examined (Fig. 3), but in three joints they alternated with regions of normal structure or of moderate hyperplasia of the synovial cells (Fig. 2). Frank necrosis of synovial cells was seen in the knee and proximal interphalangeal joint of one patient.

Haematoxylin bodies, distinct from pyknotic nuclei, were found in eleven joints. They were most common among the synovial cell nuclei (Fig. 4), but could also be seen deeper in the tissue. In one joint they were found only in the latter situation. It was sometimes necessary to search several high-power fields before the bodies were seen, but in one knee they were present in all fields of the surface layer examined (Fig. 4).

Inflammation was slight or absent. Slight to moderate infiltration with lymphocytes and plasma cells was the most severe change seen (Fig. 5, overleaf).

In two joints, oedema was the only feature. It was common to find plentiful eosinophilic material with little or no inflammatory change. Polymorphs were seen only once, in small numbers. Macrophages and fibroblasts were not seen. Despite this, six joints showed slight or moderate fibrosis of the deeper tissues (Fig. 6, overleaf).

Vascular lesions were not marked, except in one patient, who had a combination of the characteristic visceral lesions of SLE and widespread polyarteritis nodosa. Lesions of both conditions occurred in the knee examined and have been illustrated in a previous article (Cruickshank, 1952). Minor lesions,

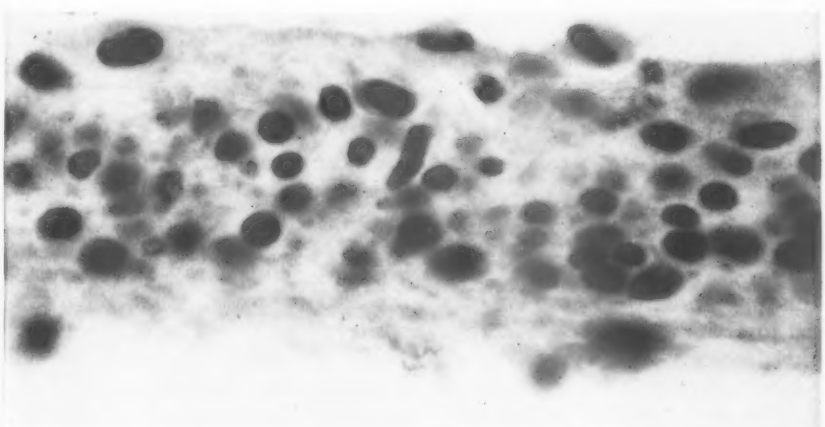


Fig. 4.—Knee: portion of a small villus, showing many small haematoxylin bodies among nuclei of synovial cells. Haematoxylin and eosin. × 650.

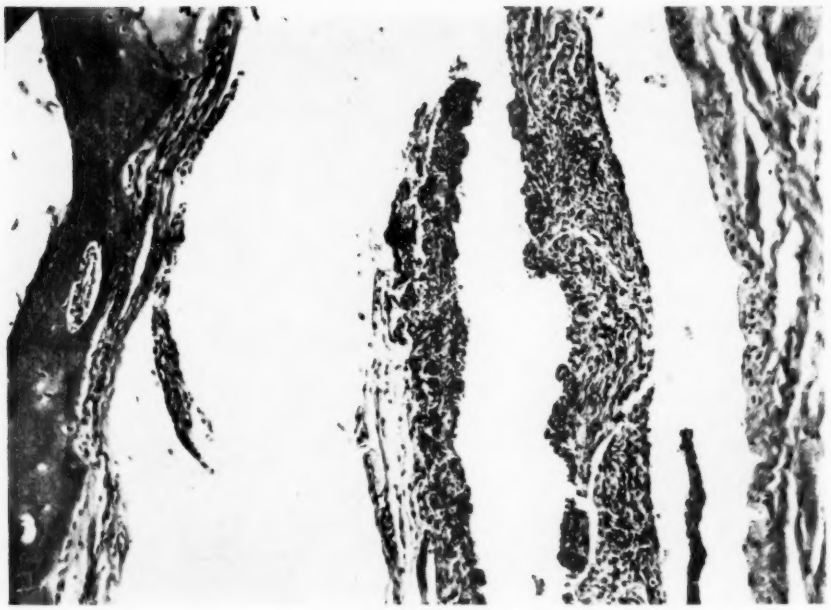


Fig. 5.—Metacarpo-phalangeal joint: slight hyperplasia of synovial cells and infiltration with lymphocytes and plasma cells. Haematoxylin and eosin. × 100.

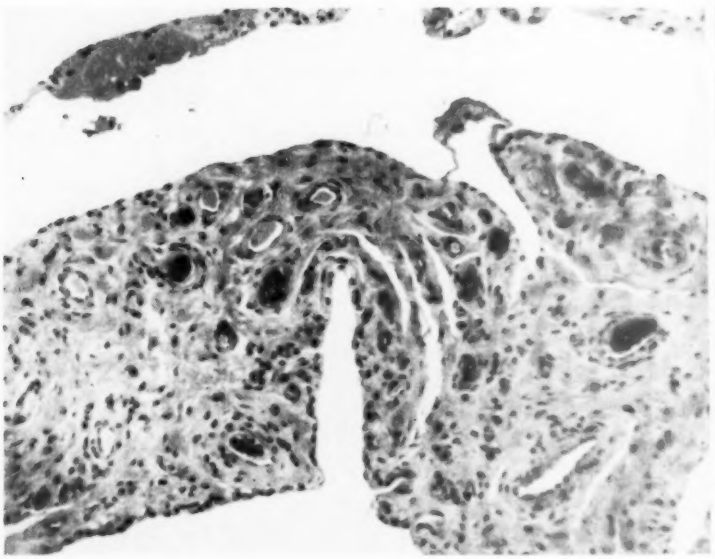


Fig. 6.—Knee (same patient as Fig. 1): diminution in number of synovial cells, fibrin-like material in upper villus, and fibrosis of larger villus. Haematoxylin and eosin. × 90.

which occurred in four other patients, included intimal fibrosis of small arteries or veins. Widespread organizing venous thrombosis was seen in the knee of one patient (Fig. 7, opposite). Recent haemorrhage was seen in this joint, and haemosiderin was seen in two other joints.

Histochemical studies were disappointing, for much of the tissue had been fixed in Helly's fluid, so that the Feulgen and methyl green-pyronin methods were unsuccessful. The eosinophilic material on and under the surface was Schiff-positive, bright red in the picro-Mallory method, and deep violet with phosphotungstic acid-haematoxylin (Fig. 2). It was not metachromatic with toluidine blue.

Articular Cartilage.—Damage was seen in five of the six finger joints. In three of these joints, there was marginal erosion with a thin layer of granulation tissue on the surface of the cartilage or on the subchondral bone plate where the cartilage had disappeared (Fig. 8, opposite). Minimal inflammation

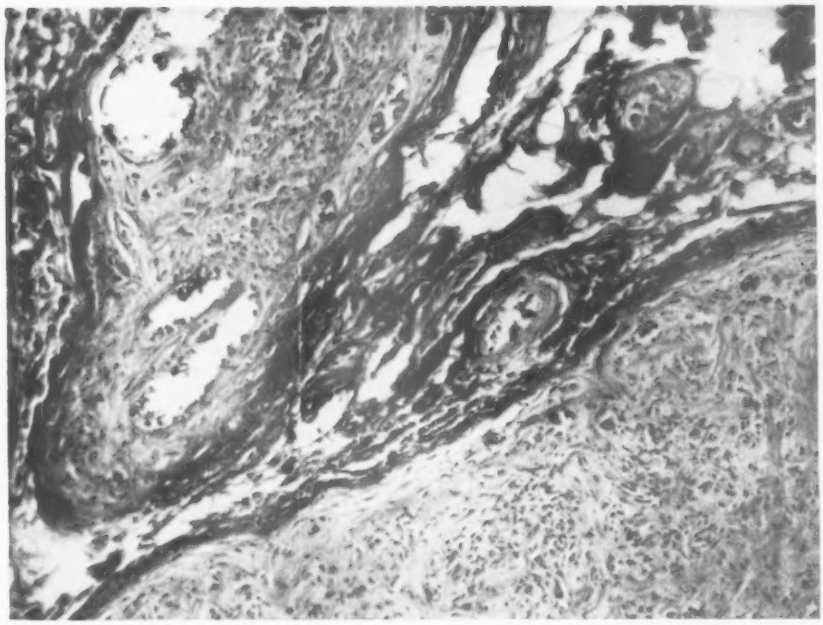


Fig. 7.—Knee (same patient as Fig. 3): two large veins completely occluded by fibrous tissue, with recanalization of one. Fibrosis of intervening venules. van Gieson. × 150.

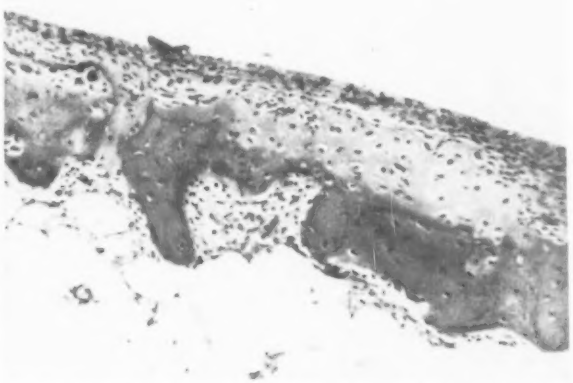


Fig. 8.—Proximal interphalangeal joint (from right hand in Fig. 1): marginal region showing loss of cartilage, thin layer of pannus on surface, and minimal involvement of underlying bone. Haematoxylin and eosin. × 70.

was seen in the immediately adjacent bone. The appearances were similar to, but less severe than, those of rheumatoid arthritis. The remaining two joints were from the hand shown in Fig. 1. Here, there was extensive loss of cartilage, sometimes with a thick layer of granulation tissue on the exposed bone (Fig. 9). The subchondral plate was thickened in places and inflammatory foci in the bone were more obvious.

Tendon-sheath Involvement.—This was seen in six of the seven patients investigated.

Fibrin-like material was present on or beneath the

Fig. 9.—Metacarpo-phalangeal joint (from right hand in Fig. 1): central region showing replacement of entire depth of articular cartilage by fibrous pannus. Haematoxylin and eosin. × 55.

surface in all six patients, often associated with a diminution in the number of synovial cells (Fig. 10). Frank necrosis was not seen.

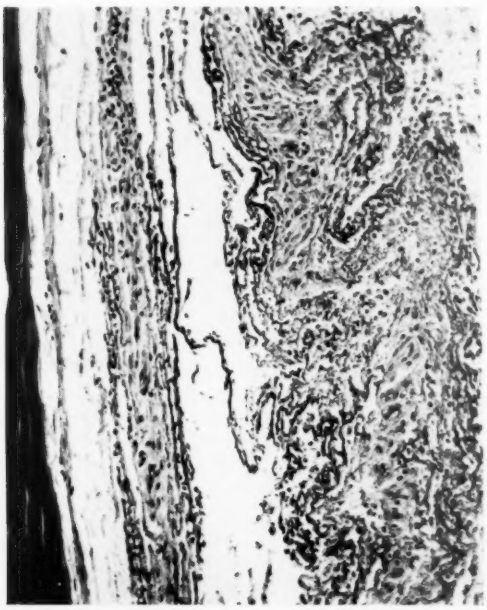
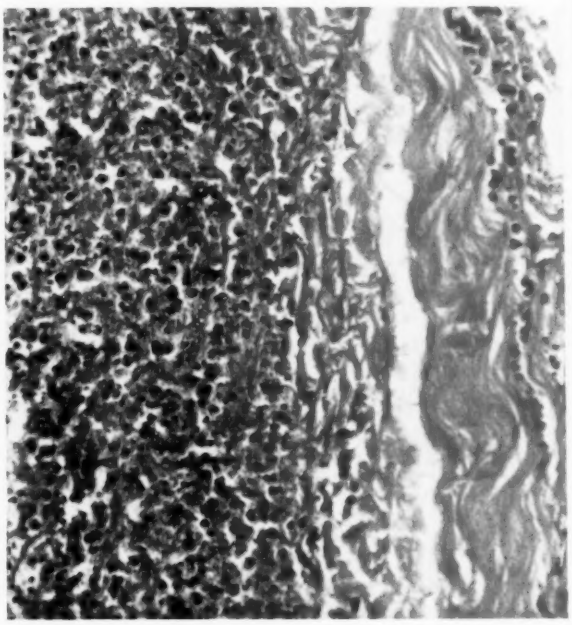


Fig. 10.—Tendon sheath: marked deposition of fibrin-like material on surface of both layers of sheath, with loss of synovial cells and minimal cellular infiltration. Haematoxylin and eosin. × 100.

Haematoxylin bodies were seen in five patients and were distributed among the synovial cell nuclei on the surface and the inflammatory cells beneath the surface (Fig. 11).

Inflammation was more marked than in the joints. In one patient it was particularly severe, acute in type, and associated with degeneration and necrosis of many of the cells of the exudate. The tendon was involved along with its sheath and there was marked disruption of the collagen fibres (Fig. 12). The remaining patients showed an

Fig. 12.—Tendon sheath: severe acute inflammation involving sheath and adjacent tendon, with necrosis of exudate and tendon. Haematoxylin and eosin. × 150.



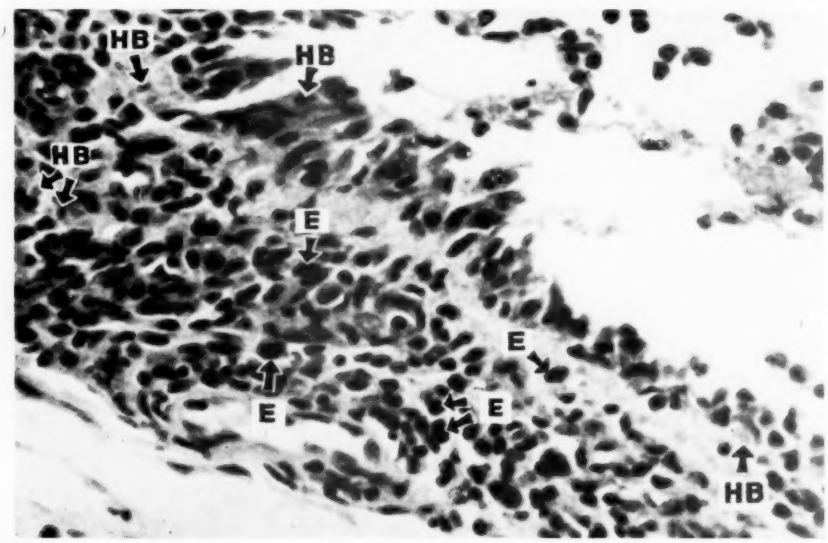


Fig. 11.—Tendon sheath (same patient as Fig. 1): infiltration with lymphocytes, plasma cells, and eosinophils (E). Haematoxylin bodies (HB) scattered among healthy nuclei. Haematoxylin and eosin. × 380.

exudate of lymphocytes and plasma cells, with occasional polymorphs and eosinophils (Figs 11 and 13).

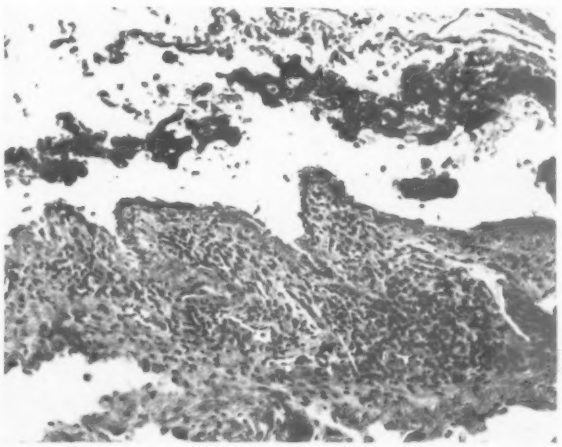


Fig. 13.—Tendon sheath (same patient as Fig. 5): fibrin-like material in space between layers of sheath and on surface of one layer. Loss of synovial cells and marked cellular infiltration. Haematoxylin and eosin. × 100.

Slight fibrosis was seen in four patients and intimal fibrosis of arterioles in two. An unusual appearance was seen in one case, the tendon sheath being nearly 2 mm. thick at one place. Here the space between the tendon and its sheath was obliterated by a nodule of large mesenchymal cells of synovial type, infiltrated with lymphocytes and plasma cells. No degeneration was seen within this nodule, nor was there any fibrosis (Fig. 14).

Histochemical studies confirmed the findings in the joints. In addition the haematoxylin bodies in two patients were shown to contain DNA (Feulgen-positive), but not RNA (pyronin-negative). DNA was not identified in the fibrin-like material in these two patients.

Discussion

These pathological changes show a number of interesting features. The presence of a layer of fibrin-like material on the surface of the synovial tissue appears to be an important feature, for it has been observed previously (Bennett and Dällenbach, 1951; Gold and Gowing, 1953; Ropes and Bauer, 1953). These and other workers (Friedberg, Gross, and Wallach, 1936; Ginzler and Fox, 1940; Bennett and Paul, 1949) have also noted that cellular evidence of inflammation was minimal or moderate. The present study confirms this. These observations suggest that the fibrin-like material may be different from that of an ordinary fibrinous exudate. Indeed, an exudate of the type in question is not seen in other forms of synovitis. The limited histochemical studies now reported suggest that the fibrin-like material is similar to the "fibrinoid" encountered in other situations in the disease (Klemperer and others, 1941). This has been shown to contain not only fibrin (Gitlin, Craig, and Janeway, 1957), but also acid mucopolysaccharide (Altshuler and Angevine, 1949), DNA (Klemperer and others, 1950), non-histone protein (Gueft and

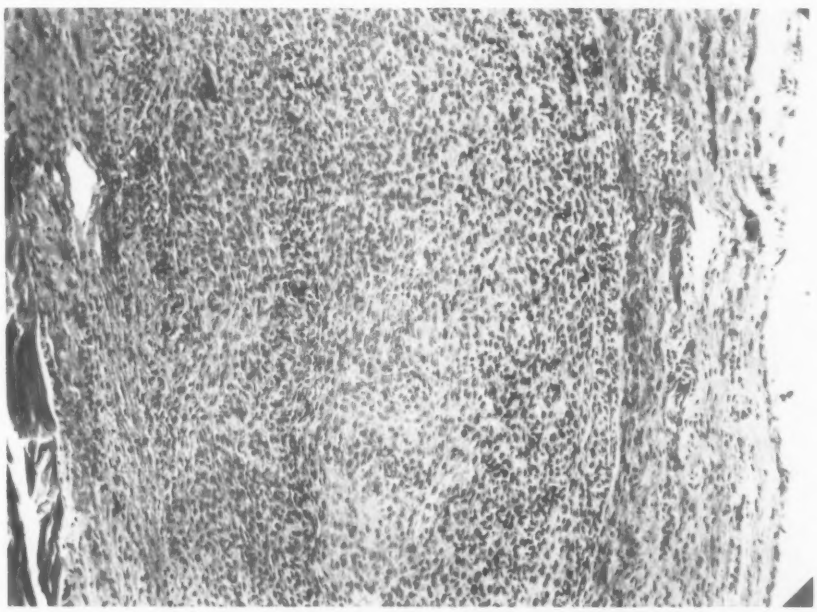


Fig. 14.—Tendon sheath (same patient as Fig. 5): focal proliferation of large mesenchymal cells and infiltration with lymphocytes and plasma cells. Haematoxylin and eosin. × 100.

Laufer, 1954), and gamma-globulin (Vazquez and Dixon, 1957, 1958). Thus the eosinophilic material on or in the synovial tissue may well be an integral part of the disease process.

Another feature which was observed in the majority of the specimens was the diminution in the number of synovial cells. Here again, the lesions of SLE differ from those of the other chronic arthritides in which proliferation of the synovial cells occurs. Bennett and Dällenbach (1951) noted this feature, and it is implied by the absence of hypertrophy of the synovial villi which is noted in all the reports, except that of Tremaine (1934). Hyperplasia of the synovial cells was observed by Zevely, French, Mikkelsen, and Duff (1956) in punch-biopsy specimens from three patients, but previous experience (Cruickshank, 1952) suggests that the small pieces of tissue obtained by this technique are not truly representative of the changes in the tissue in a chronic arthritis. The loss of synovial cells may well be due to the action of the LE factor, for haematoxylin bodies were found in most of the specimens. They are such an integral part of the pathology of the disease that it is surprising that they seem to have been observed in the synovial tissue by only two previous groups of workers (Klemperer and others, 1950; Ropes and Bauer, 1953).

Although the inflammatory changes were slight, granulation tissue (pannus) was found and was associated with loss of articular cartilage. This was usually confined to the marginal zone of the cartilage so that gross disorganization of the joints was unusual. Nevertheless, extensive loss of cartilage was seen in one patient, and had resulted in an appearance indistinguishable clinically from that of classical rheumatoid arthritis. It should be noted, however, that involvement of the subchondral bone, which is common in rheumatoid arthritis, was unusual and mild in the present material and that no evidence of adhesions or fibrous ankylosis was seen in SLE.

Vascular changes were considered to be an important feature of the synovial lesions of SLE by Lowman (1951), who described acute oedematous phlebitis in five patients, and by Ropes and Bauer (1953), who found necrotizing inflammation of small vessels with frequent fibrin thrombi in six patients. Neither of these changes was observed in the present study, but significant vascular involvement was seen twice. One patient, who had widespread polyarteritis as well as SLE, showed arterial lesions of the former in the knee. The arteritis could not be ascribed to the effect of therapy, for neither corticosteroids nor ACTH had been used, and there was no evidence of any toxic reaction to those drugs which had been administered. A second patient had widespread organizing venous thrombosis associated with marked deposition of eosinophilic material on the surface and severe oedema, but little or no cellular reaction. It seems unlikely that the thrombosis was the cause of the fibrin-like exudate, though it may well have been responsible for the oedema.

Tenosynovitis does not appear to have been described before in SLE, either clinically or pathologically. Although no clinical evidence of the changes in the present patients was obtained, it may be that other features during the terminal illnesses overshadowed any symptoms or signs referable to the tendon sheaths. The amount of fibrin-like material present in some of the tissue examined suggests that crepitus should be detectable clinically.

Most of the pathological features observed in this study are non-specific. However, it must be concluded that the combination of changes is diagnostic of SLE, for they do not occur together in any other known disease. The absence of Aschoff nodules, rheumatoid granulomata, or massive lymphocyte/plasma cell infiltration further distinguish SLE from rheumatic fever and active rheumatoid arthritis. Confusion might arise between mild or inactive rheumatoid arthritis and SLE with marked loss of cartilage, but the absence of fibrous adhesions and the presence of the surface layer of fibrin-like material in SLE, even when severe damage has occurred, should serve to differentiate the two conditions. The observation of haematoxylin bodies is the final proof of the diagnosis, for the histological and cytochemical properties of these bodies are specific (Klemperer and others, 1950; Gueft and Laufer, 1954; Godman, Deitch, and Klemperer, 1958).

Summary

Tissue was examined from fourteen joints from ten patients, and from palmar tendon sheaths from seven patients suffering from systemic lupus erythematosus.

The main lesion found in the joints was the deposition of fibrin-like material on the surface of or within the synovial tissue, associated with loss of synovial cells and haematoxylin bodies. Cellular evidence of inflammation was slight. Replacement of articular cartilage with granulation tissue occurred, but adhesions and ankylosis were not seen.

Changes in the tendon sheaths were similar to

those in the synovial tissue of the joints, though cellular infiltration was more striking.

The changes observed are individually non-specific, but collectively they differ from those of other arthritides and are diagnostic.

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Lésions des articulations et des gaines tendineuses dans le lupus érythémateux généralisé

RÉSUMÉ

On examina les tissus provenant de 14 articulations de 10 malades et de gaines tendineuses palmaires de 7 malades atteints de lupus érythémateux généralisé.

La lésion principale trouvée dans les articulations fut le dépôt d'une substance ressemblant à la fibrine, à la surface ou dans le tissu synovial, associé à une perte de cellules synoviales et de corpuscules colorés par l'hématoxyline. Il y eut peu de signes d'inflammation cellulaire. Le remplacement du cartilage articulaire par le tissu de granulation fut noté, mais on n'observa pas d'adhésions ou d'ankylose.

Les lésions des gaines tendineuses furent similaires à celles du tissu synovial des articulations, mais l'infiltration cellulaire fut plus accentuée.

Les lésions observés ne sont pas spécifiques en soi-même, mais leur ensemble les distingue des autres arthritides et les rend diagnostiques.

Lesiones de las articulaciones y de las vainas tendinosas en el lupus eritematoso generalizado

SUMARIO

Se examinaron los tejidos procedentes de 14 articulaciones de 10 enfermos y de vainas tendinosas palmares de 7 enfermos con lupus eritematoso generalizado.

La lesión principal encontrada en las articulaciones fué el depósito de una substancia de tipo de fibrina, superficial o dentro del tejido sinovial, asociado a la pérdida de células sinoviales y de cuerpos a hematoxilina. Hubo pocos signos de inflamación celular. Se notó la reposición del cartilago articular por un tejido de granulación, pero no se vieron adhesiones o anquilosis.

Las lesiones de las vainas tendinosas fueron similares a las del tejido sinovial, pero la infiltración celular fué más acentuada.

Las lesiones observadas no son específicas en si mismo, pero colectivamente difieren de otros artritides y son diagnósticas.

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TRIALS OF CORTISONE ANALOGUES IN THE TREATMENT OF RHEUMATOID ARTHRITIS

BY

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In 1954 the first report appeared of a controlled trial of aspirin *versus* cortisone in the treatment of early cases of rheumatoid arthritis (Medical Research Council-Nuffield Foundation Joint Committee, 1954). The trial showed that, after treatment for a year, the group receiving cortisone (mean dose 75 mg. daily) had fared no better than that receiving only aspirin. Some of the patients had had radiographs taken of their hands and feet at the start of the trial and at the end of the first year. Bone erosion was found to have advanced in both groups. The score for advance was slightly greater in the aspirin group, but the difference was not statistically significant. In a second trial of patients who had had rheumatoid arthritis for a mean duration of 7 years (Empire Rheumatism Council, 1955), the findings were essentially the same. Again the deterioration seen in serial radiographs was almost as much in the cortisone-treated group as in that receiving only aspirin.

Many research workers interested in the rheumatic diseases turned away from the study of corticosteroids at this point. To them corticosteroids were just non-specific suppressors of the inflammation arising from a disease process, and had no effect upon the rheumatoid process itself. Little importance was attached to the observation that a rheumatoid patient might respond well to a moderate dose of cortisone and subsequently lose the benefit gained while still on the same dose.

When the delta 1-2 analogues of cortisone and cortisol (prednisone and prednisolone) became available, further controlled trials were started. The first was a controlled trial of cortisone *versus* prednisone in rheumatoid patients who were in their second, third, or fourth year of cortisone treatment (Medical Research Council-Nuffield Foundation Joint Committee, 1957). The prednisone-treated group fared much better than the cortisone-treated group, but the significance of this finding was obscured by the relatively larger dose of prednisone given. This is well shown in Fig. 1 (opposite), which gives the mean doses, erythrocyte sedimentation rates and strengths of grip of the 21 patients from this Centre who took part in the trial. Had a 1 to 5 prednisone to cortisone dose been employed, the therapeutic superiority of prednisone, of which we are now aware, would have been apparent. More recently, fourteen patients from this trial who had been kept on cortisone for a second year were transferred to prednisolone. On this occasion the dose ratio employed was 1 to 6 prednisolone to cortisone. By the end of 6 months their mean erythrocyte sedimentation rate (Wintrobe) had fallen from 24·6 to 15 mm./hr, and their mean strength of grip had risen from 271 to 299 mm. Hg (both hands). In the previous year, while they were on cortisone therapy, there had been no change in these indices.

The second prednisone trial was for patients with rheumatoid arthritis of 3 to 24 months' duration who had not previously received corticosteroid therapy. The control group received analgesics *ad lib* (Medical Research Council-Nuffield Foundation Joint Committee, 1959). The superiority of prednisone was quickly apparent in those of our patients (21) who were in this trial. At the end of the first year practically all the radiographs that showed a marked advance in bone erosion were found to belong to the group treated with analgesics! Since many of these patients were receiving phenylbutazone, the question arose whether prednisone favourably affected the course of rheumatoid arthritis or whether phenylbutazone affected it *unfavourably*. It was easy to imagine that an analgesic like phenylbutazone relieved a lot of pain and thereby allowed destructive changes to proceed more rapidly. A comparison between the advance in bone erosion seen during phenylbutazone therapy and aspirin therapy was therefore called for; so we reviewed the radiographic changes seen in those of our patients who received aspirin in the first aspirin-cortisone trial, together with those in the patients who received aspirin in the second cortisone-aspirin trial in whom the disease was of short duration. We found that the advance in bone

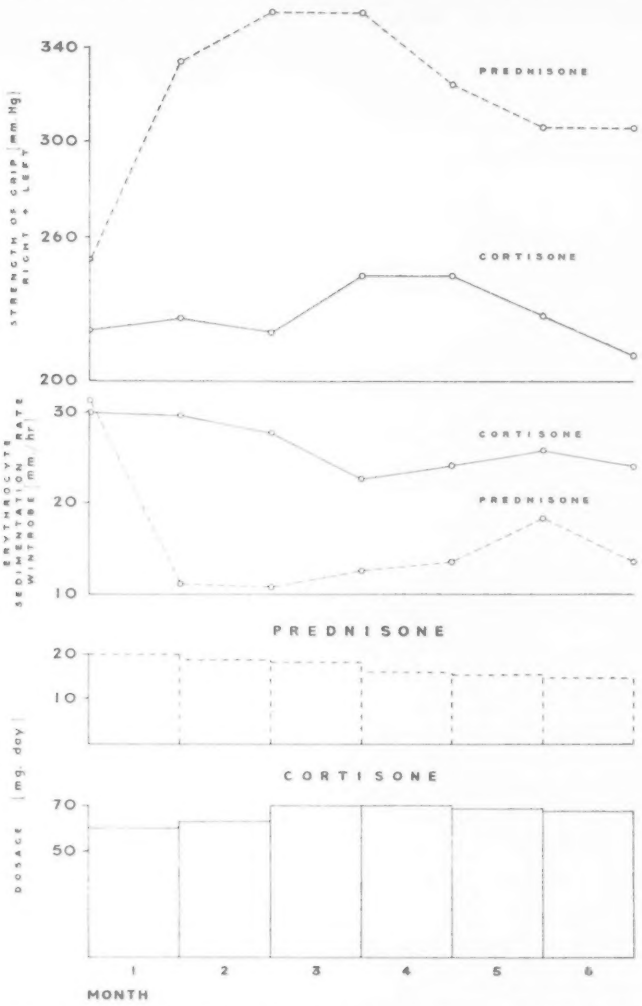


Fig. 1.—21 patients who had received cortisone for a year or more allocated at random to continue with cortisone or change to prednisone.

Mean dose, erythrocyte sedimentation rate, and strength of grip for each group for the first 6 months of the trial.

erosion during a 2-year period was of the *same order* as that seen in our patients who received phenylbutazone in the second prednisone trial.

Table I (overleaf) shows the present "*x*-ray score" for our patients in the second prednisone trial.* There thus remained little doubt that the slowing up, and in some cases arrest, of bone erosion in the prednisone-treated patients was due to the prednisone given.

Prednisone and prednisolone are the first substances shown to have a favourable effect on the course of rheumatoid arthritis, using objective data, in a fully controlled trial. Unfortunately, as is well known, they fall far short of our needs. Using the maximum safe doses for maintenance therapy, some patients with severe disease receive little relief and in the majority who do benefit the degree of benefit appears to diminish as the years go by. Further, many would say that the mean dose of prednisolone that we have used, namely 11 mg. a day, is not a safe dose. This being so, it is encumbent upon us to study each new promising cortisone analogue, in controlled trials, in the hope that one may be found that is of greater value. The questions to be asked are:

(1) Will the new analogue be effective, in a safe dose, when prednisolone has ceased to be so?

* It should be mentioned that many of the patients in the prednisone trials received prednisolone in the second and third years, since there was no evidence to suggest that prednisone and prednisolone differed qualitatively.

TABLE I

RADIOGRAPHS OF SIXTEEN PAIRS OF HANDS AND FEET FROM PATIENTS IN THE ANALGESICS GROUP AND TWENTY PAIRS OF HANDS AND FEET FROM PATIENTS IN THE PREDNISONE-PREDNISOLONE GROUP GRADED BY DEGREE OF CHANGE IN BONE EROSION SEEN AFTER MEAN INTERVALS OF 30 AND 36 MONTHS RESPECTIVELY. OBSERVED CHANGES ARE EXPRESSED AS A PERCENTAGE FOR EACH GROUP.

Therapy	Mean Interval (mths)	Change in Bone Erosions (per cent.)				
		Advance			No Change	Healing
		+++	++	+		
Analgesics, mainly Phenylbutazone ..	30	37·5	19	37·5	6	0
Prednisone-Prednisolone (mean dose 11 mg.)	36	0	20	20	55	5

(2) Will it be more effective than prednisolone *ab initio*?

(3) Will it maintain its effect for a longer period than prednisolone?

Present Investigations

Below are reports of some controlled trials of triamcinolone (16 hydroxy 9α fluoro prednisolone). It has been our experience, in the four trials mentioned above, that our own comparatively small group of participants have behaved in the same way as the total groups, so that we feel justified in drawing some conclusions from the groups of 9, 17, and 31 patients who were studied by us, and whose cases are reported in this paper.

(1) *Efficacy of Triamcinolone after Prednisolone.*—In order to answer the first question, 34 patients suffering from rheumatoid arthritis, who had been receiving prednisolone continuously for more than a year, were allocated at random to continue with prednisolone or to change to triamcinolone. In order to make a fair comparison, it was necessary to choose maximum safe dose levels for prolonged therapy for each hormone. The choice made will be considered in the discussion. Table II shows the composition of the groups after the exclusion of three patients who fell out for reasons unconnected with the trial. Certain differences were seen between the groups that may favour the triamcinolone group. A study of other similar controlled trials has shown that the overall progress is reflected most clearly in the changes in the erythrocyte sedimentation rate and in the strength of grip.

TABLE II

CHARACTERISTICS OF TREATMENT GROUPS AT BEGINNING OF TRIAL

Drug ..	Prednisolone	Triamcinolone
Number of Patients	17	14
Sex .. .. Male	6	3
Sex .. .. Female	11	11
Mean Age (yrs)	55	44½
Range (yrs)	42-67	35-60
Mean Duration of Rheumatoid Arthritis (yrs)	12½	9½
Range (yrs)	1-32	2-34
Mean Duration of Previous Prednisolone Therapy (yrs)	2	2
Range (yrs)	1-2¾	1-2¾
Mean Dose of Prednisolone before Start of Trial (mg./day)	11·2	11
Range (mg./day)	10-15	5-15
Mean Grip (mm. Hg) Right/Left	106/111	122/131
Range (mm. Hg) Right/Left	50/40-210/240	45/50-240/202
Mean Erythrocyte Sedimentation Rate (Wb) (mm./hr)	26	23·4
Range (mm./hr)	6-41	8-43
Mean Functional Capacity*	2·6	2·6

* Gradings of functional capacity from 1 to 5 as in the M.R.C./Nuffield Trials:
Grade 1 = Physically "normal" for age and sex.
Grade 5 = Bedfast and completely helpless.

Fig. 2 shows the changes in these indices in the various groups and the mean monthly doses employed. Mean haemoglobin levels and mean white blood counts did not differ significantly. The subjective estimates went slightly in favour of triamcinolone. The assessments of functional capacity remained unchanged for the prednisolone group, but improved a little in the triamcinolone group. What may be of significance is that three of the five triamcinolone patients who showed a very definite improvement relapsed in the last 2 months. Other observations made are set out in Table III.

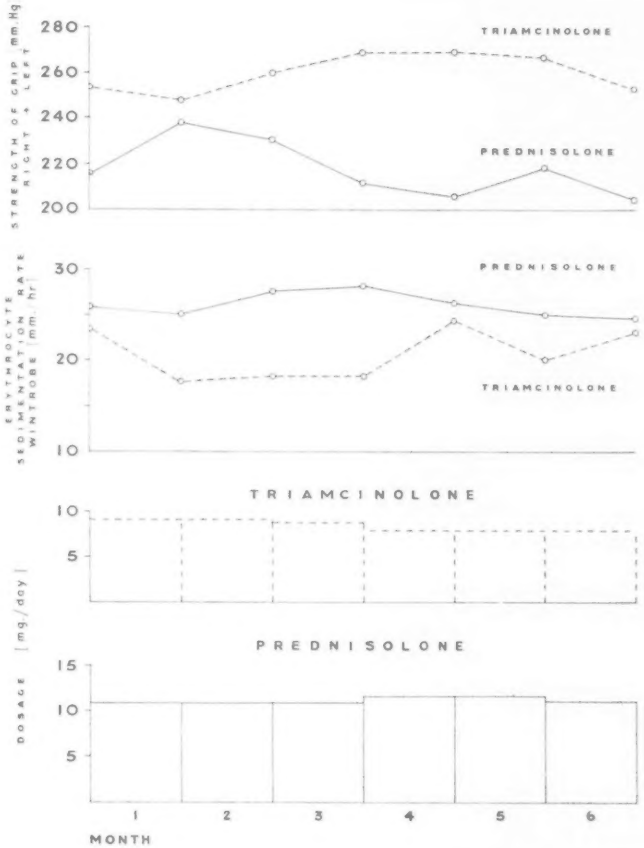


Fig. 2.—Mean monthly dose, erythrocyte sedimentation rate (Wb), and strength of grip (right hand plus left hand) for triamcinolone and prednisolone patients. The previous mean dose of prednisolone for each group is shown in Table I. The maximum grip allowed for each hand was 260 mm. Hg.

TABLE III

CHANGES IN CERTAIN CHARACTERISTICS BETWEEN WEEK 0 AND WEEK 24 IN TWO GROUPS OF PATIENTS WHO HAD HAD PREVIOUS PREDNISOLONE THERAPY

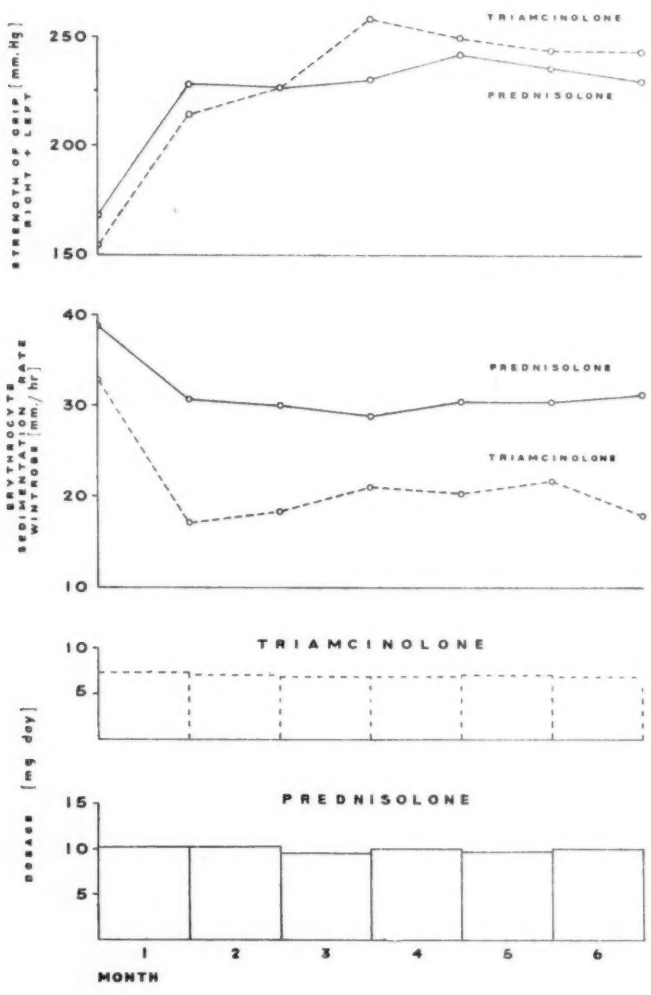
Observation	Drug	Changes Seen
Weight (kg.)	Prednisolone Triamcinolone	Rise from 64·5 to 66·4 Fall from 63 to 60
Mean Blood Pressure (mm./Hg)	Prednisolone Triamcinolone	147/90 to 150/90 149/89 to 148/89
Appetite	Prednisolone Triamcinolone	1 up; 1 down 1 up; 5 down
Dyspepsia	Prednisolone Triamcinolone	10 at start 8 at start } Slightly less in each group
Sleep	Prednisolone Triamcinolone	2 more; 2 less 2 more

TABLE IV

CHARACTERISTICS OF TREATMENT GROUPS AT START OF TRIAL

Drug		Prednisolone	Triamcinolone
Number of Patients		8	9
Sex	Male	2	2
	Female	6	7
Mean Age (yrs)		40	50
Range (yrs)		27-53	34-66
Mean Duration of Rheumatoid Arthritis (yrs)		3	5
Range (yrs)		¼-11	½-20
Mean Grip at Start of Trial (mm./Hg) Right/Left		84/83	88/66
Range (mm./Hg)		55/48-155/125	30/20-170/110
Mean Erythrocyte Sedimentation Rate (Wb) at Start of Trial (mm./hr)		39	33
Range (mm./hr)		22-56	19-55
Mean Functional Capacity*		2·75	3

* Gradings of functional capacity are as in Table II. Grade 3 = Unemployable and able to do only a limited amount of light housework.



(2) *Efficacy of Triamcinolone without Previous Corticosteroids.*—In the second trial, conducted in the same way but with patients who had received no previous corticosteroid therapy, seventeen patients were assessed monthly for 6 months. Table IV (above) shows the characteristics of the groups at the start.

Table V (opposite) shows certain changes in the characteristics between Week 0 and Week 24.

Fig. 3 depicts the monthly mean dose, erythrocyte sedimentation rate, and strength of grip.

Subjective changes were correlated with the change in erythrocyte sedimentation rate, the triamcinolone group showing a greater reduction in morning stiffness and more overall benefit. Although these patients

Fig. 3.—Mean monthly dose, erythrocyte sedimentation rate (Wb), and strength of grip for triamcinolone and prednisolone patients. All had been receiving analgesics before the trial began.

TABLE V

CHANGES IN CERTAIN CHARACTERISTICS BETWEEN WEEK 0 AND WEEK 24 IN TWO GROUPS OF PATIENTS WHO HAD HAD NO PREVIOUS CORTICOSTEROID THERAPY

Drug	Prednisolone	Triamcinolone
Erythrocyte Sedimentation Rate (Wb) (mm./hr)	39→32	33→18
Hb (g./100 ml.)	13·3→14·1	12·1→14·6
Total Leucocyte Count	8,400→8,700	8,000→8,600
Functional Capacity	2·75→2·25	3→2
Strength of Grip (mm. Hg)	84/83→112/119	88/66→116/125
Weight (kg.)	60→63	59·3→58·6
Blood Pressure (mm. Hg)	133/79→135/85	134/79→136/85

failed as a group to gain weight, four reported increased appetite and none reported a loss of appetite. The incidence of dyspepsia in each group was low.

(3) *Triamcinolone and Steroid-Induced Hypertension.*—Another trial was made to assess the effect of triamcinolone upon the blood pressure of patients who had become hypertensive during previous corticosteroid therapy. Freyberg, Berntsen, and Hellman (1958) found that the hypertension "often decreased" after triamcinolone administration.

Nine of our patients who had received prednisolone, or cortisone followed by prednisolone, for several years were transferred to triamcinolone and their blood pressures were recorded monthly. The mean blood pressure of the group before corticosteroid therapy was 135/80 mm. Hg; during the 6 months before the change to triamcinolone the diastolic blood pressure of each patient had risen to or exceeded 100 mm. Hg at least on one occasion. Fig. 4 shows the mean blood pressure and corticosteroid dose for the 6 months before and after the change over. No fall was observed during triamcinolone therapy.

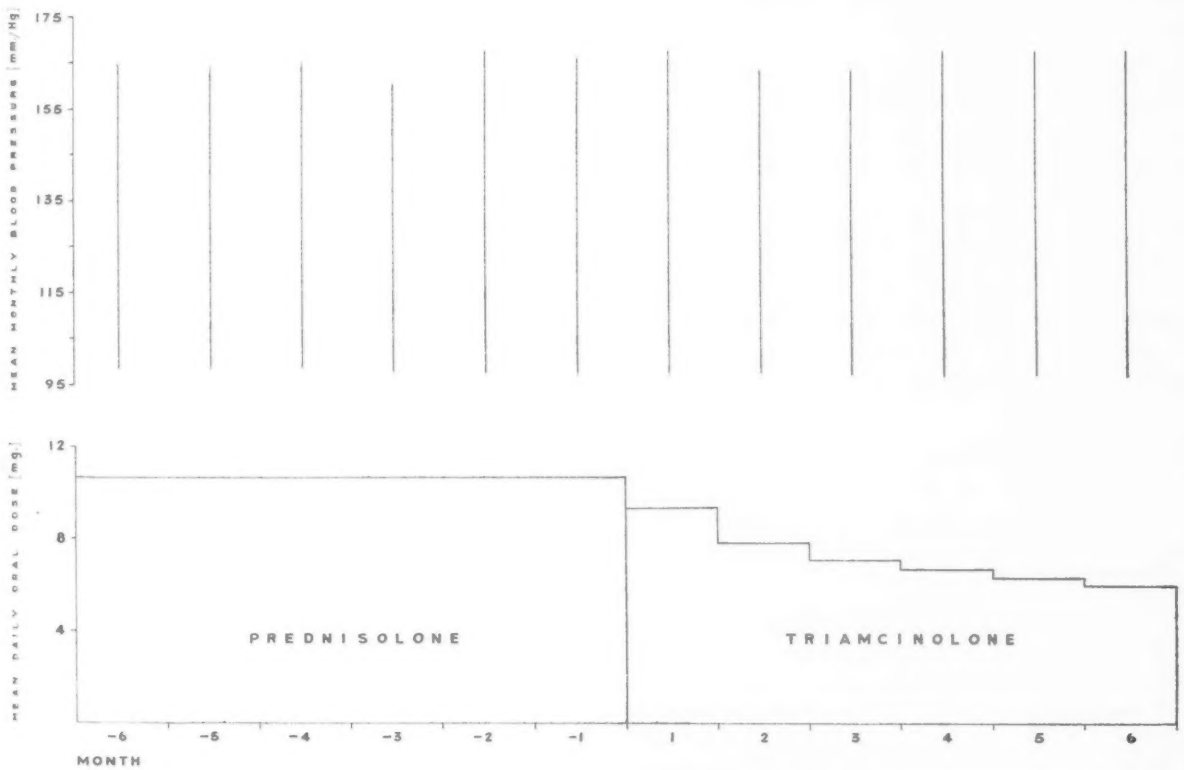


Fig. 4.—Mean blood pressure and corticosteroid dosage at monthly intervals before and after the transfer from corticosteroids to triamcinolone of nine patients whose blood pressure had risen during prolonged corticosteroid therapy.

Discussion

As no corticosteroid yet developed cures rheumatoid arthritis, we are at present concerned with finding the cortisone analogue that in prolonged use provides the most benefit without adding disease to disease. So far no new analogue has proved, in therapeutic doses, to be free from unwanted metabolic effects. This being so, it is essential that in therapeutic trials dose levels should be chosen that can be maintained safely for long periods. The varied opinions held by those who speak from experience about the value of different corticosteroids in the treatment of rheumatoid arthritis show how important it is that the trials should be "controlled".

(1) The interpretation of the first trial reported above depends upon whether 8 to 9 mg. triamcinolone are equivalent to 11 to 12 mg. prednisolone in the production of unwanted metabolic effects. No precise tally can be made of these effects when they are mild, as in this trial. Our impression is that 9 mg. triamcinolone is certainly not less productive of unwanted effects than 12 mg. prednisolone. Both amounts are at the upper limit of what we consider a safe therapeutic dose. In our opinion the findings justify the statement, in answer to the first question, that the change from prednisolone to triamcinolone has not resulted in a renewed response of the type seen when prednisolone replaces cortisone in a 1 to 5 ratio.

(2) The second trial, which was for rheumatoid arthritic patients who had not previously received corticosteroid therapy, showed the triamcinolone group at a considerable advantage when the mean dose levels were 7 mg. triamcinolone and 10 mg. prednisolone. We were not surprised at the marked improvement seen in the triamcinolone group, but had expected to see more improvement in the prednisolone group. A comparison of the characteristics of the groups at the beginning of the trial did not suggest that the prednisolone group were likely to run a less favourable course. Some readers may be surprised at the relatively small overall improvement in the prednisolone patients in view of the common saying that 60 to 70 per cent. of rheumatoid arthritic patients improve on any form of treatment. The reason for the apparent discrepancy lies in the fact that the patients we have treated with corticosteroids were not representative of rheumatoid patients as a whole but were drawn from the 5 per cent. in whom the disease appeared to be running a severe course. This trial was made to help answer the second question. If it is agreed that the doses used were the maximum safe doses for each steroid, the answer must be that triamcinolone was more effective; but it may be that the small number of patients studied does not justify this conclusion. This second trial is being continued in the hope that it will contribute to an answer to the third question.

(3) The third trial was designed to study the effect of triamcinolone on cortisone- or prednisolone-induced hypertension. Our failure to confirm the observations of Freyberg, Berntsen, and Hellman (1958) was caused, we think, by our use of a smaller dose of triamcinolone. When the original 2-mg. tablet was replaced by the 4-mg. tablet, two of our hypertensive patients received a daily dose of 16 instead of 8 mg. The blood pressure of both patients fell markedly, only to climb back to the hypertensive levels as the dose was gradually reduced to 8 mg. In the first two trials there was no significant change in the blood pressure in either group. It will be necessary to follow triamcinolone therapy for much longer than 6 months before it can be decided whether this analogue will or will not induce hypertension. It is, of course, only a minority of patients who develop hypertension during prolonged cortisone or prednisolone treatment. When prednisolone replaced cortisone it was suggested that with less salt retention there should be less hypertension, but this did not prove to be the case.

The only other "side-effect" encountered in these trials that calls for special comment was loss of weight.

It will be seen that, in the first trial, the triamcinolone patients lost, on average 3 kg. in 6 months. This loss was approved by most patients and in the majority the fall in weight appeared to have stopped by the sixth month. In the trial with previously untreated patients there was a mean fall of 0·7 kg. in the triamcinolone patients, none of whom had experienced a decrease in appetite. Some, of course, began with poor appetites. Such a group of rheumatoid arthritic patients would be below their normal weight at the start of therapy and we should expect their weight to *rise* as the disease subsided. There have been a number of reports of gross weight loss and also of muscle wasting in patients treated with triamcinolone. The fact that we have not seen such changes may be due to the moderate dose level that we have used, nevertheless, the losses in weight that we *have* seen cannot be dismissed as necessarily harmless.

Dexamethasone.—The three questions proposed at the beginning of this paper will have to be answered for dexamethasone (16-methyl 9α fluoro prednisolone). Our own trial of this very interesting hormone in patients habituated to prednisolone

therapy is collapsing through our inability to obtain, in some patients, an anti-rheumatic effect without inducing an uncontrollable weight gain. It is not possible to study these cortisone analogues without constantly speculating as to the factors that determine their diverse properties and potencies. It seems to one of us that differences in the protein-binding in the plasma of these hormones plays some part. Another factor, of more importance, concerns the mechanism in different tissues, and in different sites within these tissues, that determines the concentration of physiologically-active hormone available within the cells. Alterations in the configuration of the hormones appears to affect such concentrations from site to site in different degree. The physiological effects that follow no doubt depend upon the function of the particular tissue concerned.

Summary

Four controlled trials of cortisone and prednisone have been reviewed and some related data added.

Three trials of triamcinolone are reported:

Trial 1.—To assess the value of changing therapy from prednisolone to triamcinolone, 31 rheumatoid arthritic patients were studied who had been receiving prednisolone for from 1 to 3 years. They were allocated at random to continue with prednisolone or change to triamcinolone. The doses used, a mean of 11·5 mg. prednisolone and 8·5 mg. triamcinolone, were, in our opinion, at the upper limit of safety for prolonged administration for each hormone. The patients in each group were assessed at monthly intervals for 6 months. It was concluded that the slight apparent advantage gained by the triamcinolone patients was not such as to suggest that triamcinolone will favourably affect the course of rheumatoid arthritis when prednisolone has ceased to do so.

Trial 2.—Seventeen rheumatoid arthritic patients, who had not previously been treated with corticosteroids and who were deemed to belong to the 5 per cent. of rheumatoid arthritics in whom the disease runs a severe course were allocated at random to receive prednisolone or triamcinolone. The mean doses used were 10 mg. and 7 mg. respectively. These patients were studied in the same way as those in the first trial. The results showed a definite advantage for the triamcinolone patients. Over a 6-month period the doses used did not give rise to serious side-effects.

Trial 3.—Nine patients who had become mildly hypertensive during cortisone and prednisolone therapy were given triamcinolone instead; the mean blood pressure did not alter in the 6 months before and after the change in therapy.

One of us (H.F.W.) is the holder of a part-time research fellowship of the Nuffield Foundation. We also wish to thank Lederle Laboratories for a generous supply of Triamcinolone (Ledercort).

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Essais des analogues de la cortisone dans le traitement de l'arthrite rhumatismale

RÉSUMÉ

On passe en revue quatre essais thérapeutiques contrôlés de la cortisone et de la prednisolone et on ajoute quelques données pertinentes. On relate trois essais de la triamcinolone:

Essai I.—Pour évaluer la triamcinolone par rapport à la prednisolone administrée antérieurement, on étudia 31 malades atteints d'arthrite rhumatismale et traités par la prednisolone pendant 1 à 3 ans. On les assigna au hasard à deux groupes: l'un qui continua à recevoir de la prednisolone et l'autre qui fut transféré à la thérapie par triamcinolone. Les doses employées (11,5 mg. de prednisolone et 8,5 mg. de triamcinolone en moyenne) furent, à notre avis, à la limite supérieure de sécurité pour l'administration prolongée de chaque hormone. Dans chaque groupe, les malades furent évalués tous les mois pendant 6 mois. On conclut que le léger avantage apparent de la triamcinolone ne fut pas suffisant pour affecter favorablement l'évolution de l'arthrite rhumatismale quand la prednisolone avait cessé d'agir.

Essai II.—On étudia 17 malades atteints d'arthrite rhumatismale et censés appartenir à ces cinq pour cent des rhumatisants chez qui la maladie suit une évolution très sévère. Aucun d'entre eux n'avait reçu de corticostéroïdes auparavant. On les assigna au hasard à recevoir soit de la prednisolone soit de la triamcinolone. Les doses moyennes furent 10 mg. et 7 mg. respectivement. Les malades furent évalués de la même manière que dans le premier essai. Les résultats accordèrent un avantage défini aux malades à la triamcinolone. Les doses employées pendant 6 mois ne produirent pas d'effets secondaires sérieux.

Essai III.—Chez neuf malades, chez qui la tension artérielle avait monté un peu pendant le traitement par la cortisone et la prednisolone, on substitua la triamcinolone; la tension artérielle moyenne ne changea pas pendant 6 mois qui précédèrent ou se succédèrent au changement thérapeutique.

Ensayos de los análogos de la cortisona en el tratamiento de la artritis reumatoide

SUMARIO

Se pasan en revista cuatro ensayos terapéuticos controlados de la cortisona y de la prednisolona y se añaden algunos datos pertinentes. Se relatan tres ensayos de la triamcinolona.

Ensayo I.—Para valorar el cambio terapéutico de la prednisolona a la triamcinolona, se estudiaron 31 enfermos con artritis reumatoide tratados con prednisolona por uno a tres años. Estos enfermos fueron repartidos al azar en dos grupos: uno que siguió con prednisolona y el otro que fué tratado con triamcinolona. Las dosis empleadas (11,5 mg. prednisolona y 8,5 triamcinolona en promedio) aproximáronse, a nuestro juicio, a los límites superiores de seguridad para la administración prolongada de cada hormona. En ambos grupos los enfermos fueron valorados cada mes durante seis meses. Se llegó a la conclusión de que la pequeña ventaja aparente de la triamcinolona no fué suficiente para afectar favorablemente la evolución de la artritis reumatoide, cuando la prednisolona había cesado de actuar.

Ensayo II.—Se estudiaron 17 enfermos con artritis reumatoide, perteneciendo aparentemente a aquel cinco por ciento de los reumáticos en que la enfermedad sigue una evolución muy severa. Ninguno de ellos había recibido corticoesteroides anteriormente. Se les asignó al azar al tratamiento sea con prednisolona, sea con triamcinolona. Las dosis medias fueron de 10 mg. y de 7 mg. respectivamente. Los enfermos fueron valorados del mismo modo que en el primer ensayo. Los resultados fueron netamente mejores en los enfermos tratados con triamcinolona. Las dosis empleadas durante seis meses no produjeron efectos secundarios serios.

Ensayo III.—Triamcinolona fué administrada a nueve enfermos en los cuales la tensión arterial había subido algo durante un tratamiento previo con cortisona o prednisolona. No se observó cambio alguno de la tensión arterial media en estos enfermos seis meses antes o después de cambiar el tratamiento.

Ann. Rheum. Dis. (1959), **18**, 129.

METABOLISM OF CONNECTIVE TISSUE IN LIMB ATROPHY IN THE RABBIT

BY

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In previous experiments in adult rats (Slack, 1954, 1955), massive tissue atrophy was induced by denervation and femoral head dislocation of one hind limb. A study of the metabolism of total collagen, total sulphated polysaccharide, and mixed muscle protein indicated that disuse atrophy does not imply cessation of all protein or polysaccharide synthesis. After the onset of atrophy some synthesis of collagen appears to continue for at least 15 weeks. Synthesis of muscle protein continues for about 6 weeks and of sulphated polysaccharide for at least 2 weeks. The interesting finding was that at least some of the normal synthetic processes continue despite massive removal of muscle protein and connective tissue.

These earlier experiments did not differentiate between connective tissue closely associated with the muscle mass, and connective tissue in the bones, joints, and associated tendon insertions. Furthermore, the rat experiments were open to objection because of the unusual operative technique required to achieve aseptic atrophy, and the fact that the bones of the rat appear to be capable of growth throughout much of the life of the animal. In view of the unexpected finding of continued connective tissue synthesis in the atrophying rat limb it was considered desirable to repeat the experiments in a larger animal.

In the present experimental work, to be described, atrophy has been induced in one hind limb of rabbits by denervation. The metabolism of connective tissue collagen fractions and sulphated polysaccharide has been studied in two limb components: connective tissue associated with the muscle mass (soft tissue compartment), and that in bones, joints, and tendon insertions (skeletal compartment).

Both the present work, and the previous experiments in rats, are concerned with disuse atrophy. Gillespie (1954) showed that, in a paralysed limb the main factor in atrophy is, in fact, disuse. Diminution of blood supply is not a controlling factor. It also appears from his work that the bony changes in the paralysed limbs are due to quantitative differences, and not to alterations in quality of the bones—as judged by breaking stress, elasticity, percentage of ash, and specific gravity. *X* rays show a loss of density in disused limb bones, described as decalcification or osteoporosis. Gillespie's work shows that these terms may be misleading.

More recently Geiser and Trueta (1958) have described changes in the calcaneum of the rabbit, atrophying as the result of tendo calcaneus section, plaster immobilization, and other means. Bone removal was found to occur up to 5 or 6 weeks after the onset of atrophy. Thereafter there appeared to be little further bone removal. This time-interval corresponds to the time required for complete muscle atrophy and cessation of muscle protein synthesis in the rat experiments quoted above (Slack, 1954). It is interesting that Geiser and Trueta, in their experiments, found evidence of osteoblasts *at all stages of atrophy*. In other words, some synthesis of new connective tissue must be occurring in the bone despite overall atrophy. This finding is in agreement with the experiments on collagen metabolism in atrophying rat limbs quoted earlier.

A considerable volume of work has been published on changes in muscle proteins following denervation, tenotomy, and plaster fixation. The interested reader is referred to Helander (1957) for an excellent review and results of original work. The impact of atrophy on the connective tissues appears still to be receiving less attention than it deserves. It is hoped that the experiments to be described will, in some measure, add to our knowledge of connective tissue behaviour in massive tissue atrophy.

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Experimental Methods

Operative Procedure

Young adult rabbits weighing 1·8 to 2 kg. were subjected to neurectomy under ether anaesthesia and local nerve blocks. In each case an attempt was made to transect, and remove at least a distal one inch of, all motor nerves to the left hind limb. The approach was made ventrally, just lateral to the lower spine, and the sympathetic supply dissected out. Of the animals surviving operation, one-third proved to have incomplete denervation and are not included in this series. Successful operations produced a complete flail left hind limb, showing obvious muscle atrophy from the hip level downwards.

Administration of Isotopes and Separation of Tissues

14 days after operation, six rabbits, selected for complete paralysis of the left hind limb, were injected subcutaneously in the upper abdomen with 10 μc. α-^{14}C glycine per 100 g. body weight, and 200 μc. $Na_2{}^{35}SO_4$ per 100 g. body weight. The rabbits were then killed serially from 10 hours after isotope injection to 4 days afterwards.

The skin was stripped from both hind limbs down to the toes, which were cut off. The limbs were cut through and dislocated at the level of the femoral head. All muscle and associated fascia from each limb was removed, and this constituted the soft tissue compartment. The tissue samples were reduced to a homogeneous powder by repeated freezing in liquid nitrogen and pounding in a steel mill. After removal of aliquots for determination of total constituents the tissue fractions were separated as follows:

Collagen Fractions.—Neutral salt-soluble collagen, acidic citrate-soluble, and insoluble collagens were separated and purified, essentially as described by Jackson (1957).

The collagen content of the separated fractions was estimated by the method for hydroxyproline given below.

Sulphated Polysaccharide.—All material remaining, including supernatants, from each stage of collagen fractionation was treated as described in other experiments (Slack, 1958). The method has been shown to give good recovery of sulphated polysaccharide free from protein or hyaluronic acid (Scott, 1955). As isolated, the polysaccharides are therefore those soluble in neutral salt, acid citrate buffer, and 0·1 N NaOH, free or associated with tissue protein in the natural state. The associated protein was hydrolysed by treatment with papain to facilitate its removal.

Separated polysaccharide was estimated gravimetrically. Chemical analyses of the acetone dried preparations were done, to determine sulphate and hexosamine contents, as described below.

Chemical Analyses

Hydroxyproline.—Estimated by the Neuman and Logan method as modified by Miyada and Tappel (1956).

Hexosamine.—Determined by the method of Boas (1953).

Sulphate.—Estimated according to the method described in a previous communication (Slack, 1958).

Radioactivity Measurements

Collagen.—Preparation and isolation of 2:4 dinitro-phenylglycine was as described by Neuberger, Perrone, and Slack (1951). Radioactivities were determined on solid samples of "negligible thickness" according to the method of Henriques, Henriques, and Neuberger (1955), or on solid samples of "infinite thickness" when quantities in excess of 25 mg. crystalline DNP-glycine were available.

Sulphate.—This was separated as the 4-chloro-4′-amino diphenyl derivative and radioactivities were determined as previously described (Slack, 1958).

Results

2 weeks after neurectomy total wasting in the atrophying left limb amounted to 23 per cent. in terms of the weight of the normal right hind limb. The greater part of this wasting occurred in the soft tissues (Table I, opposite); 16 weeks after operation loss of tissue in the atrophying limb amounted to 44 per cent., but at 19 weeks it had increased only to 47 per cent. These figures are similar to the rates of total tissue wasting found in the rat (Slack, 1954).

The amounts of collagen fractions obtained are shown in Table II (opposite). As expected, the greater part of the collagen was in the insoluble phase. Neutral salt-soluble collagen formed only a very small part of the total collagen. The amounts obtained after final purification were so small as to present analytical difficulties. Quantitative and radioactivity measurements on the neutral salt-soluble fraction of collagen are probably therefore subject to greater experimental variation than either of the two remaining collagen fractions. Consistently smaller amounts of neutral salt-soluble collagen were obtained from the atrophying limbs.

TABLE I

WET WEIGHT OF WHOLE TISSUES IN NORMAL AND ATROPHYING RABBIT LIMBS
14 DAYS AFTER NEURECTOMY AND 16 TO 19 WEEKS AFTER
(Percentage wasting expressed as percentage difference from the opposite normal limb)

Time Interval after Neurectomy (wks)	Serial No. of Rabbit	Normal Right Hind Limb			Atrophying Left Hind Limb		
		"Tissue Compartment"		Total	"Tissue Compartment"		Total
		Skeletal	Soft		Skeletal	Soft	
2	1001	41	124	165	38	86	124
	1002	32	108	140	28	69	97
	1003	38	147	185	36	96	132
	1004	30	120	150	29	85	114
	1005	39	135	174	36	100	136
	1007	48	132	180	45	86	131
	Average	38	128	166	35	87	122
	Percentage Wasting				8	32	23
16	974	47	149	196	36	72	108
	975	38	121	159	31	59	90
	Percentage Wasting						44
19	986	30	90	120	23	41	64
	987	32	108	140	26	50	76
	Percentage Wasting						47

TABLE II

AMOUNTS OF COLLAGEN FRACTIONS, AND COMPARISON OF TOTAL SEPARATED FRACTIONS WITH TOTAL COLLAGEN IN ORIGINAL MATERIAL
(Collagen contents determined by the method of Miyada and Tappel (1956))

Serial No. of Rabbit	Material	Separated Collagens (g./100 g. fresh tissue)								Total Collagen in Original Material (B)		Difference between A and B as percentage of B	
		Neutral Salt-soluble		Acidic Citrate-soluble		Insoluble		Total (A)					
		Skeletal	Soft	Skeletal	Soft	Skeletal	Soft	Skeletal	Soft	Skeletal	Soft	Skeletal	Soft
1001	Normal	0·0029	0·0021	1·35	0·36	23·2	2·09	24·5	2·45	26·9	2·95	10	17
	Atrophying	0·0020	0·0014	1·53	0·81	18·7	1·50	20·2	2·31	27·5	3·61	26	36
1002	Normal	0·0032	0·0024	1·05	0·39	22·1	3·36	23·1	3·75	26·2	4·41	12	15
	Atrophying	0·0021	0·0012	1·23	0·56	19·5	2·29	20·8	2·85	27·0	4·80	23	40
1003 and 1004	Normal	0·0021	0·0022	1·14	0·32	22·6	1·87	23·8	2·19	26·4	2·72	10	20
	Atrophying	0·0018	0·0010	1·35	0·54	20·6	1·61	21·9	2·15	27·9	3·38	21	36
1005 and 1007	Normal	0·0027	0·0020	1·22	0·31	23·1	3·00	24·3	3·00	27·4	3·70	13	23
	Atrophying	0·0017	0·0013	1·68	0·60	19·9	1·57	21·6	2·16	28·5	4·06	25	46

By contrast, larger amounts of acid citrate-soluble collagen were obtained from both skeletal and soft tissue compartments of the atrophying limbs. The insoluble collagen requires special attention.

Insoluble collagen, separated from fresh tissues as described, was found to be smaller in amount per unit weight atrophying limb as compared with the opposite normal limb. On the other hand, total collagen estimated by hydroxyproline was higher per unit weight of tissue in the atrophying limb (Table III, overleaf). The hydroxyproline figures agree with previous experience (Harkness, 1957; Slack, 1954), and it is therefore probable that the extraction procedures used have resulted in a greater loss of purified collagen in the case of atrophying tissue. Reference to the final column of Table III shows that some 15 per cent. of the initial total collagen was lost by the extraction procedure on normal tissues. In atrophying tissue at least 25 per cent. was lost. In general, the atrophying soft tissue showed a greater loss than the skeletal tissue. Some of the difference between estimated total collagen and collagen fractions separated and isolated in the atrophying limbs can be accounted for by increased acid citrate-soluble fraction. But the greater part of the collagen lost

TABLE III

AMOUNTS OF SULPHATED POLYSACCHARIDES RECOVERED FROM SKELETAL AND SOFT TISSUES OF NORMAL AND ATROPHYING HIND LIMBS OF RABBITS 14 DAYS AFTER NEURECTOMY

(Amounts determined gravimetrically on acetone-dried specimens)

Serial No. of Rabbit	Material	Sulphated Polysaccharides* (mg./100 g. fresh tissue)						Total Separated Polysaccharide	
		Neutral Salt Extract		Acidic Citrate Extract		0·1 N NaOH Extract			
		Skeletal	Soft	Skeletal	Soft	Skeletal	Soft	Skeletal	Soft
1001	Normal	19	12	6	4	108	33	133	49
	Atrophying	14	19	4	9	80	23	98	51
1002	Normal	24	19	14	10	126	40	164	69
	Atrophying	16	18	10	11	112	32	138	61
1003 and 1004	Normal	22	11	12	7	110	42	144	60
	Atrophying	19	16	18	3	66	36	103	55
1005 and 1007	Normal	16	7	13	5	94	38	123	50
	Atrophying	7	15	8	7	79	22	94	44

* Analyses of separated polysaccharides gave figures for sulphate content varying from 10·2 to 12·9 g./100 g. polysaccharide, and of hexosamine 24·2 to 33·6 g./100 g. polysaccharide.

in the extraction procedure seems to result from altered stability of insoluble collagen at the stage of 0·1 N NaOH extraction.

The amounts of sulphated polysaccharide recovered from the tissues are shown in Table III. In most cases there was a decrease in polysaccharide in the atrophying tissues, both as recovered fractions of polysaccharide and as measured by total hexosamine. There was, however, considerable variation in the actual amounts of polysaccharide recovered per unit weight fresh tissue in normal and atrophying limbs. The variations were such as to permit only a general statement that atrophying tissue, both skeletal and soft, shows some reduction of total polysaccharide per unit weight of fresh tissue.

The data obtained on the metabolism of collagen are given in Table IV. These are admittedly scanty. From the available figures it would appear that the greater reduction of synthesis of collagen occurred in the neutral salt-soluble fraction. The synthesis of this precursor fraction was reduced in both skeletal and soft tissue. At 14 days after neurectomy the greatest reduction in new synthesis of precursor collagen was evidenced in the soft tissues (Fig. 1, opposite). But, despite this reduction in synthesis of new collagen, *all* the neutral salt fractions of collagen from the atrophying tissues showed some evidence of continuing synthesis of collagen.

From Table IV it is also evident that some newly-synthesized collagen becomes incorporated in both the insoluble collagen fraction and the acid citrate-soluble fractions. The figures do not permit of further evaluation beyond the fact that some incorporation of new glycine is being achieved in these collagen fractions, even during active atrophy of the limb tissues.

TABLE IV

SPECIFIC RADIOACTIVITIES OF COLLAGEN FRACTIONS FROM SKELETAL AND SOFT TISSUES OF NORMAL AND ATROPHYING HIND LIMBS OF RABBITS 14 DAYS AFTER NEURECTOMY

Serial No. of Rabbit	Time after Isotope	Material	Collagen Radioactivities*					
			Neutral Salt-soluble		Acidic Citrate-soluble		Insoluble	
			Skeletal	Soft	Skeletal	Soft	Skeletal	Soft
1003 and 1004	10 hrs	Normal	581	1,324	65	23	31	7
		Atrophying	320	344	28	38	47	41
1005 and 1007	24 hrs	Normal	174	374	180	110	39	15
		Atrophying	102	120	148	192	57	56
1001	2 days	Normal	68	150	218	147	71	30
		Atrophying	54	56	315	234	85	46
1002	4 days	Normal	14	20	144	92	80	31
		Atrophying	38	26	342	246	98	59

* Counts derived from $\alpha^{14}C$ labelled glycine and radioactivity expressed as count/min./mg. collagen.

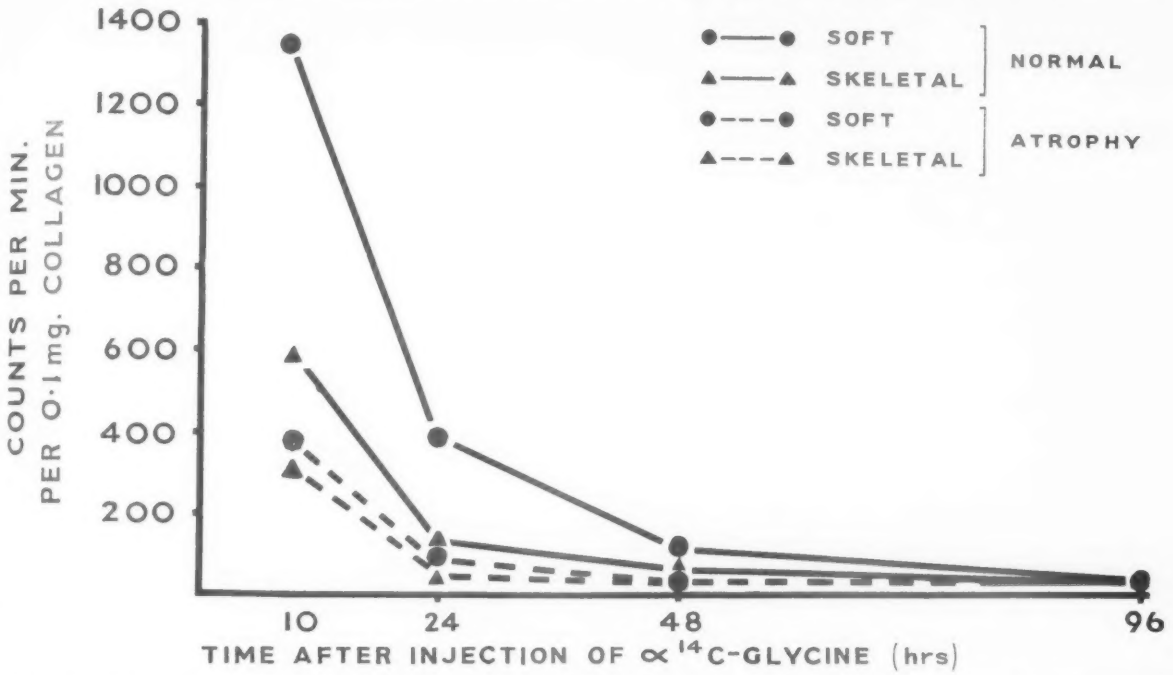

Fig. 1.—Specific activities of α[14]C-DNP glycine in neutral salt-soluble collagen from skeletal and soft tissues of atrophying left hind limbs, and normal right hind limbs, of rabbits, 14 days after operation.

The amounts of sulphated polysaccharide recovered from the tissues are shown in Table III and their specific activities in Table V. The quantities shown in Table III are acetone dried weights of separated polysaccharides. A series of total hexosamine estimations were done on aliquots of original material. These indicated that the amounts of polysaccharide actually obtained in a relatively pure state were of the order of only one-tenth of that presumably present on the basis of total hexosamine estimation. By no means all the hexosamine in total tissue samples derives from mucopolysaccharide, but the polysaccharide actually recovered from the tissues may well be only a portion of that bound to connective tissue proteins in the living tissue.

The polysaccharide extracted from the tissues by neutral salt was small in relation to the total extracted polysaccharide, but showed relatively high specific activity in both normal and atrophying

TABLE V

SPECIFIC RADIOACTIVITIES OF POLYSACCHARIDE SULPHATE IN THREE EXTRACTS OF SKELETAL AND SOFT TISSUES OF NORMAL AND ATROPHYING HIND LIMBS OF RABBITS 14 DAYS AFTER NEURECTOMY

Serial No. of Rabbit	Time after Isotope	Material	Radioactivities*					
			Neutral Salt Extract		Acidic Citrate Extract		0·1 N NaOH Extract	
			Skeletal	Soft	Skeletal	Soft	Skeletal	Soft
1003 and 1004	10 hrs	Normal	686	774	9	6	190	25
		Atrophying	525	470	12	12	266	9
1005 and 1007	24 hrs	Normal	620	542	22	12	461	272
		Atrophying	585	481	40	32	310	39
1001	2 days	Normal	505	409	37	10	342	119
		Atrophying	551	462	28	20	280	90
1002	4 days	Normal	200	237	22	5	206	33
		Atrophying	307	351	36	24	249	110

* Radioactivity expressed as count/min./0·1 mg. sulphate.

limbs. There was no unequivocal evidence of a marked reduction of metabolic activity in this fraction from the atrophying limbs. But how much of this polysaccharide fraction was bound to neutral salt-soluble collagen, and how much to the tissue proteins, is at present uncertain.

The acidic citrate extract of polysaccharide appears to have similar specific activity-time relations to the alkali extract, but the specific activities were much smaller at all intervals of time.

By far the greater part of the total polysaccharide was not liberated until the final stage of extraction with 0·1 N alkali. This portion of the polysaccharide was that bound by insoluble connective tissue proteins. The specific activities (of this bound polysaccharide) were higher in the skeletal fractions than in the soft tissue, but in all cases much less than the specific activity found in the neutral salt-extractable polysaccharide. The figures suggest a lower rate of turnover of this polysaccharide fraction from the soft tissues in the atrophying limb, and some reduction in specific activity in the skeletal compartment (Fig. 2).

Discussion

From the limited evidence of these experiments and from previous work (Slack, 1954), it seems clear that massive tissue atrophy does not imply a complete cessation of connective tissue synthesis. As might be expected, there does seem to be a reduction of synthesis of both collagen and polysaccharide in both skeletal and soft tissues of the atrophying limb.

This reduced synthesis is most evident in the soft tissues at 14 days of atrophy. Since the soft tissues are atrophying at a much greater rate than the skeletal compartment this finding is not surprising. In the case of collagen, the greatest reduction of synthesis occurs in the neutral, salt-soluble, precursor collagen of the atrophying limb. Both the acidic citrate-soluble and insoluble collagens also show some evidence of a reduced rate of metabolic turnover.

It is regrettable that insufficient polysaccharide could be isolated from the precursor collagen fraction to permit adequate analysis. There does appear, however, to be a marked difference in metabolic behaviour between the main polysaccharide (0·1 N alkali) fractions from skeletal and soft tissues. In the skeletal tissue the main bulk of polysaccharide from the atrophying limb shows evidence of continuing synthesis in substantial amounts. On the other hand, that from the soft tissues of the atrophying limb shows definite evidence of a slowing down of synthesis.

From these and earlier experiments in the rat

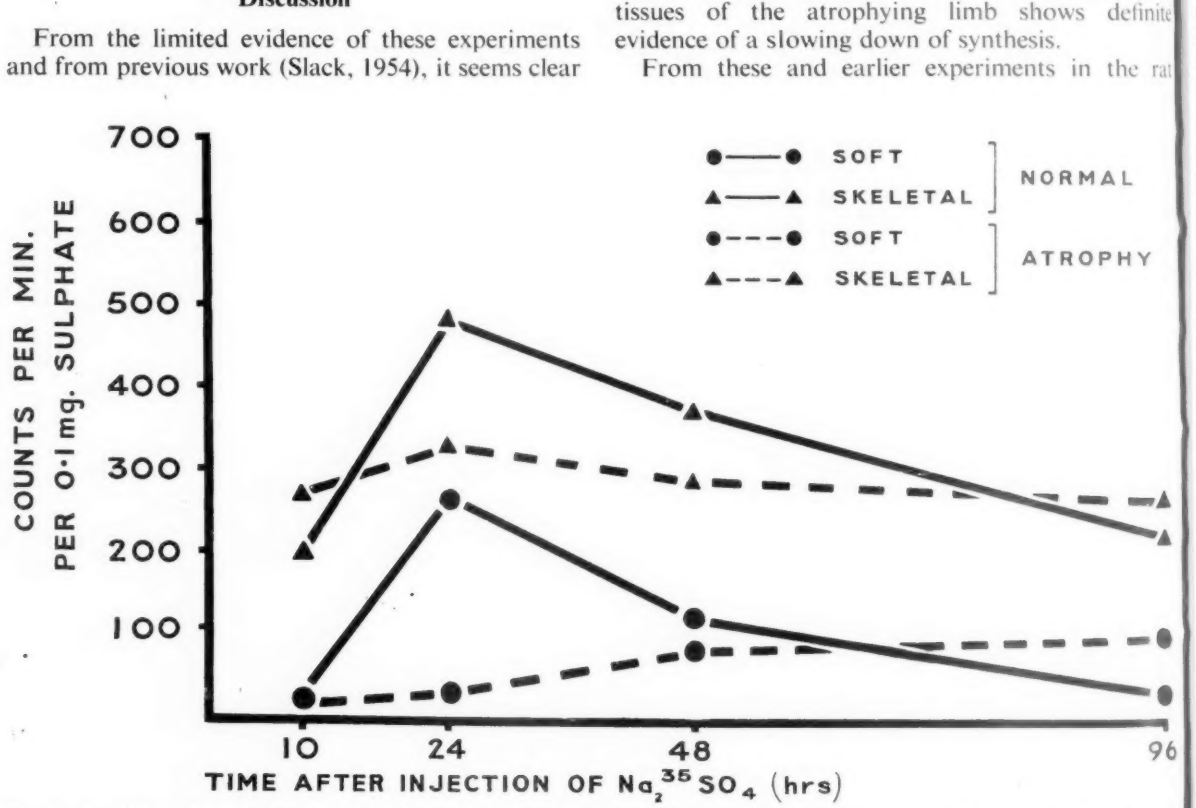

Fig. 2.—Specific activities of $^{35}SO_4$ in polysaccharide extracted by 0·1 N NaOH from skeletal and soft tissues of atrophying left hind limbs and normal right hind limbs, of rabbits, 14 days after operation.

(Slack, 1954), and from the work of Gillespie (1954), Geiser and Trueta (1958), and others, it seems clear that massive tissue atrophy is a metabolically active process. It would seem to be an energy-requiring process. Therefore, a continued blood supply, and some continuing synthesis of new connective tissue components would appear, ordinarily, to be an essential requirement.

Summary

(1) Massive tissue atrophy was achieved in the left hind limb of six rabbits by extensive neurectomy and sympathectomy.

(2) 14 days after operation, α^{14}C-glycine and ^{35}S labelled sodium sulphate were injected subcutaneously, and the animals were killed at 10 hrs, 24 hrs, 2 days, and 4 days afterwards.

(3) From the atrophying limb and opposite normal limb in each case, the tissues were separated into a soft tissue compartment (muscle, fascia, and tendon) and a skeletal compartment (bones, joints, and tendon insertions).

(4) Collagen was separated in three fractions: neutral salt-soluble precursor collagen, acidic citrate-soluble collagen, and insoluble collagen. Sulphated polysaccharide was separated in three similar fractions.

(5) In the case of collagen, there is evidence of continued synthesis in both skeletal and soft tissues of the atrophying limbs. The most marked reductions in metabolic activity were found in the soft tissue compartment (which is atrophying most rapidly), and particularly in the neutral salt-soluble collagen.

(6) The main portion of the sulphated polysaccharide, the final alkali-soluble fraction, also shows some reduced metabolic activity, most marked in the soft tissues. The behaviour of polysaccharide associated with the precursor collagen could not be assessed.

(7) The findings provide additional evidence that, although synthesis of collagen and polysaccharide is almost certainly reduced in massive tissue atrophy, there is no complete cessation of these processes.

We wish to thank Prof. J. H. Kellgren for many suggestions and continued encouragement, and Miss K. Broady and Mr. D. Myhill for their technical assistance.

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Métabolisme du tissu conjonctif dans l'extrémité atrophiée du lapin

RÉSUMÉ

(1) On provoqua une atrophie massive des tissus de la patte postérieure gauche de six lapins par des neurectomies et sympathectomies étendues.

(2) Quatorze jours après l'opération, on injecta par voie souscutanée les radio-isotopes ^{14}C-glycine et ^{35}S sulfate de soude et on sacrifia les animaux 10 heures, 24 heures, 2 jours et 4 jours plus tard.

(3) Dans tous les cas les tissus de la patte atrophiée et de la patte correspondante normale furent divisés en partie molle (muscle, fascia et tendon) et squélettique (os, articulation et insertion tendineuse).

(4) Le collagène fut divisé en trois portions: collagène précurseur, soluble en présence de sel neutre, collagène soluble en présence de citrate acide et collagène insoluble. Le polysaccharide sulfaté fut divisé en trois portions similaires.

(5) En ce qui concerne le collagène, on trouva des indices que sa synthèse continue aussi bien dans le tissu squélettique que mou des extrémités atrophiées. L'activité métabolique la plus réduite fut constatée dans la partie comprenant du tissu mou (qui s'atrophie le plus rapidement), et particulièrement dans le collagène soluble en présence de sel neutre.

(6) La portion principale du polysaccharide sulfaté, celle qui se dissout finalement dans l'alcali, accusa aussi une réduction de l'activité métabolique, plus marquée dans les tissus mous. On ne put pas déterminer le comportement du polysaccharide associé au collagène précurseur.

(7) Ces résultats offrent des preuves additionnelles montrant que, bien que la synthèse de collagène et de polysaccharide soit presque certainement réduite dans une atrophie massive des tissus, elle ne cesse pas entièrement.

Metabolismo del tejido conjuntivo en la extremidad atrofiada del conejo

SUMARIO

(1) Se produjo una atrofia masiva de los tejidos de la pata trasera izquierda de seis conejos por neurectomias y simpatectomias extensas.

(2) Catorce días después de la operación se inyectaron por vía subcutánea los radio-isótopos ^{14}C-glicina y ^{35}S sulfato de sodio y los animales fueron sacrificados 10 horas, 24 horas, 2 días y 4 días después.

(3) En todos los casos los tejidos de la pata atrofiada y de la pata correspondiente normal fueron divididos en dos partes: una blanda (músculo, fascia y tendón) y la otra esquelética (hueso, articulación e inserción tendinosa).

(4) El colágeno fué dividido en tres porciones: colágeno precursor, soluble en presencia de sal neutra, colágeno soluble en presencia de citrato ácido y colágeno insoluble. El polisacarido sulfatado fué dividido en tres porciones similares.

(5) En el caso de colágeno, encontráronse indicios

de que su síntesis continua tanto en el tejido esquelético como en el blando de las patas atrofiadas. La mayor reducción de la actividad metabólica fué encontrada en el tejido blando (que se atrofía más rápidamente), particularmente en el colágeno soluble en presencia de sal neutra.

(6) La porción principal del polisacarido sulfatado, aquella que se disolve finalmente en el álcali, también acusó una reducción de la actividad metabólica, más pronunciada en los tejidos blandos. No se pudo determinar el comportamiento del polisacarido asociado al colágeno precursor.

(7) Estos resultados ofrecen datos adicionales mostrando que, aunque la síntesis del colágeno y del polisacarido se vea casi ciertamente reducida en una atrofia masiva de los tejidos, este proceso no cesa enteramente.

Ann. rheum. Dis. (1959), **18**, 137.

EFFECT OF ASPIRIN ON CUTANEOUS RESPONSE TO THE LOCAL APPLICATION OF AN ESTER OF NICOTINIC ACID

BY

LESLIE H. TRUELOVE AND J. J. R. DUTHIE

From the Rheumatic Unit, Northern General Hospital, Edinburgh

"Trafuril"* is the trade name of a cream containing 5 per cent. by weight of tetrahydrofurfuryl nicotinic acid ester in a water-miscible base. The cutaneous reaction which follows the local application of this substance has been described by Strehler (1949). It is characterized by the appearance, within 10 to 30 minutes, of erythema usually accompanied by superficial oedema.

Nassim and Banner (1952) made the interesting observation that this response was absent in patients with active rheumatoid arthritis. In less acute cases, a mild erythema only was produced. In those with minimal evidence of activity or in remission, a normal or subnormal response was the rule. The diminished skin reaction in a proportion of patients with rheumatoid disease was subsequently confirmed by Oka (1953), Vaillancourt (1954), and Bartfeld and Hartung (1954). In these reports no mention was made of whether the patients were being treated with aspirin at the time of testing. Leifer and Batterman (1955) could detect no difference between the reactions in a group of patients with rheumatoid arthritis and in a comparable group of patients with a variety of other diseases. The majority of arthritic patients were stated to be receiving salicylates as an analgesic agent.

During an investigation of the effects of aspirin on experimentally-induced erythema, "Trafuril" was applied to the forearm of patients with rheumatoid arthritis who were not taking aspirin. The subsequent reaction was similar to that seen in healthy controls. On the basis of these observations it was decided to study in more detail the effect of aspirin on the reaction to "Trafuril" in normal subjects and in patients with rheumatoid arthritis.

* Manufactured by Messrs. Ciba Ltd.

Material and Methods

Tests were made on healthy hospital staff and on patients in hospital suffering from "definite" rheumatoid arthritis according to the diagnostic criteria proposed by the American Arthritis and Rheumatism Foundation (Ropes, Bennett, Cobb, Jacox, and Jessar, 1956). They were on a basic regimen consisting of rest in bed, splinting of affected joints, and physiotherapy. Initially all were receiving aspirin in doses of 60-80 gr. daily.

The ester was used in the form of the 5 per cent. "Trafuril" cream, or as a 5 per cent. solution in 0·15 M sodium chloride.

Tests were made by applying approximately 120 mg. "Trafuril" cream uniformly to an area one inch in diameter on the volar surface of the forearm, or by applying the solution to a similar area of skin.

Reactions were graded as follows:

0—No erythema
1—Erythema without oedema
2—Erythema and oedema

Aspirin was given by mouth in the form of tablets which produced 5 gr. calcium aspirin when dissolved in water. Solutions for intradermal injection were prepared by dissolving calcium aspirin in 0·15 M sodium chloride. The pH was adjusted to between 7 and 8 by the addition of 0·1 M sodium hydroxide.

Aspirin and free salicylate in the blood were estimated by the method described by Smith (1951).

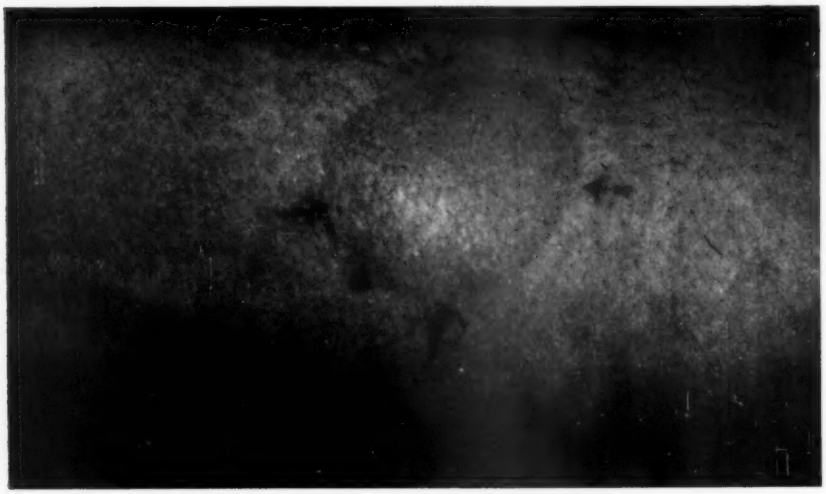

Fig. 1.—Reaction after an application of ester—Grade 1.

Fig. 2.—Reaction after an application of ester—Grade 2.

Results

Characteristics of the Reaction.—Application of "Trafuril" cream to the skin of healthy subjects resulted in the appearance of a punctate erythema within 5 to 10 minutes. The erythema rapidly became confluent and covered an area corresponding exactly to the site of application (Fig. 1). Superficial oedema then developed (Fig. 2), and in most subjects the area became surrounded by a flare. The reaction reached its maximum intensity in half an hour and faded gradually thereafter. The erythema persisted for a further 4 to 5 hours.

Strehler (1949) observed a considerable variation in sensitivity between individuals and this was confirmed. However, the sensitivity of an individual did not vary significantly from day to day. It was therefore considered justifiable to compare the results of testing the same individuals on successive days. Identical results were obtained whether tests were made with the cream or the solution.

Chilling of the skin before application of the "Trafuril" resulted in a diminished response, and for this reason experiments were performed at room temperature above 20° C.

Effect of Aspirin by Mouth on the Reaction in Normal Subjects.—A series of single tests in normal individuals showed that a dose of 10 gr. calcium aspirin by mouth resulted in partial suppression of the reaction when "Trafuril" was applied 1 hour later. A proportion of subjects in these tests showed erythema arising at the site of application of the "Trafuril" from 2 to 3 hours later. Ten normal subjects were therefore given 10 gr. calcium aspirin by mouth and a standard application of the ester was made 1 hour later. The reactions were read after half an hour and thereafter hourly for the following 5 hours. A control group of ten subjects was similarly tested. The results are illustrated in Fig. 3 (opposite).

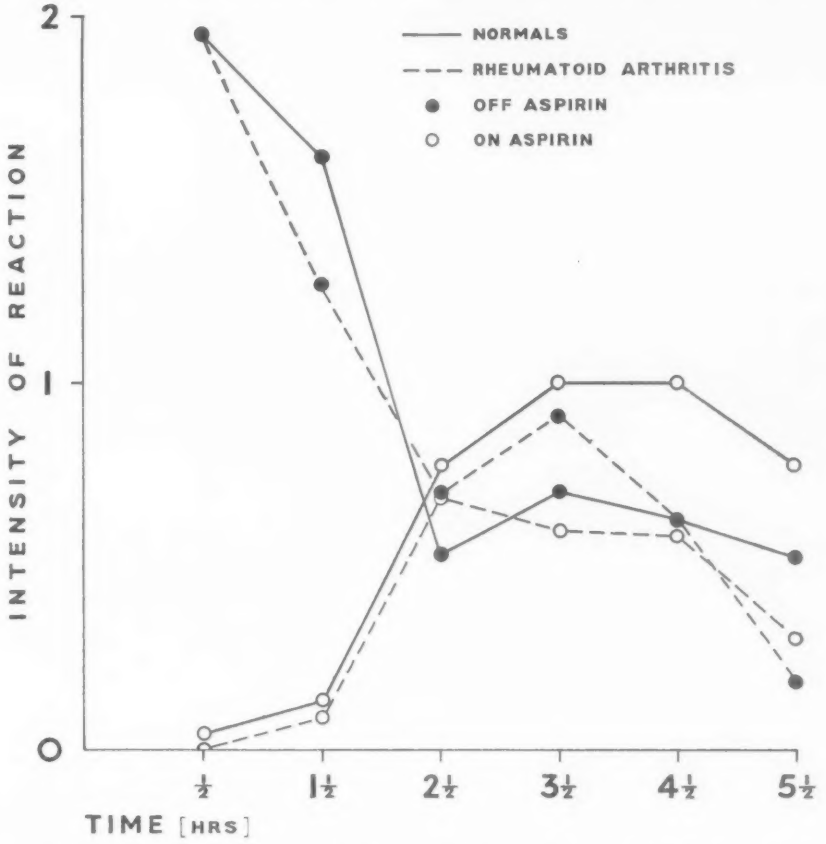

Fig. 3.—Mean response in normal and rheumatoid subjects after a single application of ester.

The greatest difference between the groups was observed half an hour after the application of the ester. At this time the subjects who had been given the aspirin showed pallor or faint blueness at the site of application (Fig. 4, overleaf).

Erythema developed in this area after 2 to 3 hours (Fig. 5, overleaf), and subsequently there was no distinction between the subjects who had been given aspirin and those who had not. The delayed appearance of erythema was not due to excretion of the aspirin as the initial phase of the reaction to the ester re-applied at this stage was still suppressed.

Effect of Aspirin by Mouth on the Reaction in Patients with Rheumatoid Arthritis.—A similar experiment was performed on ten patients with rheumatoid arthritis. Treatment with aspirin was stopped for 3 days before the test; 5 per cent. "Trafuril" cream was used and the reactions recorded as in the previous experiment. The administration of aspirin was then resumed and the tests repeated the following day. The results are shown superimposed on those of the previous experiment in Fig. 3. They do not differ from those recorded in normal subjects.

Oedema was never observed in the delayed type of reaction seen when aspirin had been administered before the test.

Local Effect of Aspirin on Reaction to "Trafuril".—0·1 ml. of a solution of calcium aspirin containing 4 mg./ml. was injected intradermally into the forearm. "Trafuril" cream was applied to the area 1 hour later. When the reaction was read after a further half hour, an area of pallor 20 mm. in diameter was apparent surrounding the site of injection (Fig. 6). This area became erythematous after a further 2½ hours and was then no longer distinguishable from the surrounding erythema. Injection of 0·1 ml. of 0·15 M sodium chloride had no such effect. An injection containing one-tenth of the dose of aspirin produced a rather smaller area of modified response (Fig. 6, overleaf).

Effect of Variations in Dose of Aspirin.—In normal subjects a single dose of 10 gr. calcium aspirin by mouth was always sufficient to cause suppression of the immediate reaction to "Trafuril". An attempt was made to determine the lowest dose of aspirin sufficient to achieve this effect and to correlate this dose with the levels of aspirin and free salicylate in the blood. Thirteen normal subjects were given doses of calcium aspirin by

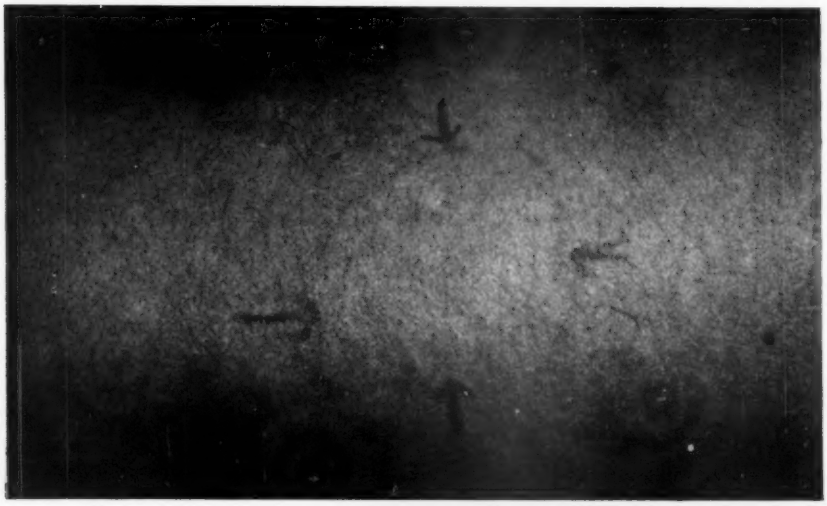

Fig. 4.—Modified reaction after 10 gr. aspirin by mouth.

Fig. 5.—Delayed erythema. The same site as Fig. 4, 3 hours later.

Fig. 6.—Local effect of aspirin on reaction to "Trafuril".

mouth varying from 2·5 to 10 gr. and were tested at varying times later. The results showed that suppression of the early phase of the reaction could be complete even when aspirin or free salicylate could not be detected in the blood and that this effect persisted for 24 hours or longer.

Discussion

The response to "Trafuril" applied to the skin of normal subjects has been described. Patients with rheumatoid arthritis who were not receiving aspirin showed a similar reaction. Furthermore, both patients and controls showed a characteristic modification of the response when aspirin was given by mouth. There can be little doubt that the abnormal response in patients with rheumatoid arthritis previously reported was due to the ingestion of aspirin.

Consideration of the effect of aspirin on the characteristics of the reaction suggests that there are two phases: an early phase of erythema, oedema, and surrounding flare, fading in $1\frac{1}{2}$ to $2\frac{1}{2}$ hours, and a later phase of erythema alone. Aspirin appears to exert its effect on the early phase of the reaction. It may be noted that oedema was never a feature of the late phase of the reaction.

Modification of the early phase around the site of an intradermal injection of aspirin is evidence in favour of the idea that the drug has a direct local action. The continued suppressive effect of aspirin for as long as 24 hours after a small dose by mouth, when it can no longer be detected in the blood, suggests fixation by the tissues.

Further work is in progress to determine whether aspirin is effective in modifying erythema or oedema induced by other agents, and whether other drugs claimed to have an anti-inflammatory action can modify the reaction to the nicotinic acid ester in a similar way.

The mode of action of this ester in producing erythema and oedema on direct application to the skin is unknown. The evidence available at present (Strehler, 1949; Oka, 1953) does not suggest that the reaction is due directly to release of histamine or that aspirin is anti-histaminic. However, it seems reasonable to suppose that the action of aspirin demonstrated in these experiments may bear a relationship to its therapeutic effect in the treatment of such conditions as rheumatic fever and rheumatoid arthritis.

Summary

(1) The characteristics of the reaction induced in normal skin by the application of the tetrahydrofurfuryl ester of nicotinic acid have been described.

(2) The reaction in patients with rheumatoid arthritis who are not receiving aspirin differs in no way from the normal.

(3) The early phase of the reaction is significantly modified in both normal and rheumatoid subjects by the administration of aspirin by mouth and by the intradermal injection of soluble aspirin before application of the ester.

(4) It is suggested that the action of aspirin demonstrated in these experiments may be related to its therapeutic effect in the treatment of diseases such as rheumatic fever and rheumatoid arthritis.

During the period when this work was done, the Rheumatic Unit was in receipt of grants from the Nuffield Foundation, the Medical Research Council, and Boots Pure Drug Company Limited.

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Effet d'aspirine sur la réponse cutanée à l'application locale d'un ester d'acide nicotinique

RÉSUMÉ

(1) On décrit les caractères de la réaction provoquée dans la peau normale par l'application de l'ester tetrahydrofurfuryl d'acide nicotinique.

(2) La réaction des malades atteints d'arthrite rhumatismale et recevant de l'aspirine ne diffère aucunément de la réaction normale.

(3) La phase précoce de la réaction se voit modifiée appréciablement chez des sujets aussi bien normaux que rhumatisants par l'administration d'aspirine par voie buccale ou par l'injection intradermique d'aspirine soluble avant l'application de l'ester.

(4) On suggère que l'action de l'aspirine mise en évidence dans ces expériences serait associée a son effet thérapeutique dans des maladies telles que le rhumatisme articulaire aigu et l'arthrite rhumatismale.

Efecto de aspirina sobre la respuesta cutánea a la aplicación local de un ester de ácido nicotinico

SUMARIO

(1) Se describen los rasgos de la reacción provocada en la piel normal por la aplicación del ester tetrahidrofurfuril de ácido nicotínico.

(2) La reacción de los enfermos con artritis reumatoide recibiendo aspirina no difiere de manera alguna de la reacción normal.

(3) La fase temprana de la reacción se ve alterada apreciadamente tanto en sujetos normales como en reumáticos por la administración de aspirina por vía oral o de aspirina soluble por vía intradérmica antes de la aplicación del ester.

(4) Se sugiere que la acción de la aspirina, evidenciada en estos experimentos, pudiera estar asociada a su efecto terapéutico en enfermedades del tipo de reumatismo poliarticular agudo o de artritis reumatoide.

Ann. rheum. Dis. (1959), **18**, 142.

EMPIRE RHEUMATISM COUNCIL

TWENTY-SECOND ANNUAL REPORT

The 22nd Annual Report of the Empire Rheumatism Council was presented by the Chairman, Dr. W. S. C. Copeman, at the Annual General Meeting, held on April 30, 1959, at the House of Lords.

National Appeal

The appeal for the £250,000 research fund, under the chairmanship of the Rt. Hon. the Lord Astor of Hever, had continued to make good progress.

The Rt. Hon. the Lord Kindersley and Mr. G. Tyser had kindly agreed to become joint Hon. Treasurers, and had made approaches to Industry which had already resulted in the fund passing the half-way mark.* A great deal of support had been given in the form of donations under deeds of covenant or promises of annual payments for periods of 7 to 10 years. Such support was very valuable, as it enabled research projects to be undertaken which would take some years to complete.

Research†

Population Studies.—A mobile *x*-ray department and laboratory had been constructed through the generosity of the Wellcome Foundation. The Council had appointed Dr. J. S. Lawrence as full-time director of this mobile field unit, provided secretarial and technical staff, and purchased an estate car for use during surveys, both for home visiting and for the transport of patients to the *x*-ray centre.

In association with the Pneumoconiosis Research Unit of the Medical Research Council, a field survey had been carried out in the Rhondda Valley in South Wales.

The latest field survey was being carried out in Wensleydale in Yorkshire. The information obtained from this rural area would be of great interest to compare with data from the industrial area of Leigh, Lancs., which had been surveyed previously. It was proposed to examine and test over a thousand persons, many of them living on isolated farms.

It was the intention of the Council to carry this type of investigation into industry with the object of finding evidence of the effect of various types of employment on the rheumatic diseases. Preliminary material which was being studied with the co-operation of the Trades Unions had been obtained from mills owned by Fine Spinners and Doublers Ltd., the Brownlow Fold Mill in Bolton, and the factory of Platt Bros. in Oldham.

The new information already gained from these field surveys made it clear that this type of work was of the greatest value in rheumatism research.

Satisfactory diagnostic criteria for use in population studies had been evolved, employing radiological and serological as well as clinical techniques, and the Field Unit with its unique experience of studying random population samples had become an international reference centre, surveys in other countries being increasingly modelled on the techniques developed here. Dr. J. S. Lawrence was also arranging for the interchange of serum samples and *x*-ray films taken in other centres so that truly comparable statistics might be made available from other parts of the world.

Similar surveys were already in progress in Holland, and the Field Unit had been consulted by workers planning surveys in Australia, New Zealand, and Finland. The closest collaboration was also maintained with colleagues in America. The *x* rays from the populations surveyed in Lancashire, Yorkshire, South Wales, and Scotland had been re-studied after randomization, and the results were being analysed for publication. These studies would provide the first accurate figures of the geographic distribution of rheumatoid arthritis and osteo-arthritis.

Connective Tissue Studies.—For the last 4 years Dr. Madeline Keech, at the University of Leeds, had been studying with the electron microscope the changes which take place in collagen and elastin, two important constituents of connective tissue, and their reaction to various enzymatic and physical agents.

Another E.R.C. Fellow, Dr. A. G. Lloyd, in the Department of Biochemistry of the University of Wales, was conducting studies of the synthesis and degradation of chondroitin sulphate, an important constituent of cartilage. The Council had provided his department with a spectrophotometer in order that this work might proceed more speedily. A third E.R.C. Fellow, Dr. J. Thomas, was working at the Low Temperature Research Station at Cambridge on the isolation, purification, and determination of the specificity of proteolytic and mucolytic enzymes acting on components of connective tissue.

In the University of Wales, Dr. P. Fourman had been investigating the effect of the injection of certain substances such as chondroitin sulphate and hormones of the parathyroid gland on organs such as the kidney and blood vessels. It was hoped to elucidate the little-understood mechanism of alteration in those parts which

* A list of the chief donors is included in the printed report (pp. 25 and 26).

† A report on *Progress in Rheumatism Research* by the Hon. Medical Secretary, Dr. Oswald Savage, appears on pp. 14-18 of the Annual Report, which may be obtained from the Secretary, Mr. M. C. G. Andrews, Faraday House, 8 Charing Cross Road, London, W.C.2. The Mobile Field Unit is fully described on pp. 20-21.

had been seen to occur in long-standing cases of rheumatoid arthritis.

These studies were often referred to as "long-term research projects" because progress in those meticulous fields of investigation must inevitably be slow. It was impossible to attract the greatest experts in basic research unless sufficient time could be allowed for a project to be carefully planned and carried through. It had therefore been the policy of the Council to elect research Fellows for at least 2 years, almost always continued for a further year, and to provide special equipment and other necessary help where required.

Blood Changes.—The agglutination reactions in the blood of patients with rheumatoid arthritis and associated diseases, demonstrated by such tests as the Rose-Waaler (sheep-cell agglutination) test, were being investigated by the Mobile Field Unit, and the Council was also financing other studies on the same theme.

At the University of Birmingham, a project was being started under Professor J. Squire with the object of studying blood proteins by electrophoresis, the ultracentrifuge, and immunochemical methods. Financial help was also being given to Dr. D. M. Weir at the Canadian Red Cross Memorial Hospital, Taplow, Bucks, to assist his investigations of a specific factor which reacts with cell nuclei in diseases such as disseminated lupus erythematosus and rheumatoid arthritis. Although this important factor had not yet been completely characterized, a great deal of evidence had accumulated about it and further studies were clearly needed.

Osteo-Arthritis.—At the London Hospital, Dr. M. Wilkinson, in collaboration with Sir Russell Brain, was studying changes in the cervical vertebrae (cervical spondylosis), particularly in their association with disseminated sclerosis and its relation to injury and to pains in the upper limbs.

Professor D. H. Collins of the University of Sheffield was studying the metabolic activity of hyaline cartilage in the different parts of the body, with particular emphasis on the rate of synthesis of chondroitin sulphate. He was aiming to correlate his findings with the pathological changes of osteo-arthritis.

At St. George's Hospital, London, Mr. P. French was investigating the changes of early osteo-arthritis of the knee joint in material obtained from patients in whom the condition was so severe that exploration of the joint had become necessary.

Pain.—Professor C. A. Keele, of the Department of Pharmacology, Middlesex Hospital, London, had been working on the problem of pain for some years, and had extracted from human blood a pain-producing substance in the form of the polypeptide. The Council had given financial support to Dr. V. Eisen, who was working in this department, to enable him to carry out further work on this substance.

Drugs.—Dr. Douglas Robertson, of the Biochemical Department of the West London Hospital, was studying procedures by which it was hoped to overcome the undesirable effects of the cortisone-like group of drugs, and to explain their mechanism of action.

Dr. D. Abelson and Dr. I. C. Gilliland, at the Postgraduate Medical School, London, were working on the same problem by comparing the rate of disappearance of hydrocortisone from the blood of patients with rheumatoid arthritis and other conditions.

The most commonly used drug in "rheumatism" was aspirin or some other derivative of the salicylates. Its mode of action was still unknown and the Council was financing two efforts to find this out: those of Dr. V. Moses at King's College Hospital, who was studying the effect of salicylates and other anti-rheumatic drugs on the chemical changes in tissue, and those of Dr. J. A. Hicklin at the London Hospital, who was studying the action of the same drug on tissue metabolism and permeability.

Chair of Rheumatology.—The Council's second chair of Rheumatology had been founded during the year at London University, and it had been agreed to finance it for a period of 10 years. Professor E. G. L. Bywaters had been appointed the first holder of the Chair at London University and the Council had also agreed to support financially the research projects which he was carrying out.

Travelling Fellowships.—Research workers and others had been sent to study overseas through the generosity of the Geigy Pharmaceutical Co., Ltd. Mr. W. D. Coltart, F.R.C.S., spent two valuable months in the United States, and Dr. E. Hess went to study at the University of Texas Southwestern Medical School under Dr. Morris Ziff for a period of one year. It had been decided to extend these Fellowships to allow research workers from the Commonwealth to visit the United Kingdom.

Equipment.—The most notable contribution during the year was an automatic chromatogram strip scanner, costing some £850 for the University of Cardiff. It was being used in connexion with the Fellowship held by Dr. Lloyd.

Clinical Trials.—The controlled trial of gold therapy in rheumatoid arthritis involving 27 centres, which was started in 1957, had been continued during the year and would not be completely analysed until late in 1959.

Education

The Council had decided to issue to all general practitioners in the National Health Service, quarterly "Reports on the Rheumatic Diseases". These were being issued for a trial period of 18 months starting at the beginning of 1959, after which the G.P.'s opinion of them would be asked. The Council was confident that this service would prove valuable both to the G.P. and to his patient.

Symposium.—In October a symposium was held at the Royal Society of Medicine in conjunction with the Association of Industrial Medical Officers. The interest

in this field was evident from the large number of Medical Officers who attended.

Handbooks.—Many requests had been received from doctors for the Council's two handbooks for patients (*Rheumatoid Arthritis* and *Osteo-Arthritis*) and publication was to be continued. A third handbook on *Rheumatic Fever* was being prepared.

The Council had also issued a card for patients who were receiving steroid treatment. In cases of accident or emergency it was essential that it should be known that the patient was undergoing steroid therapy, and this card would give all the information required. The Ministry of Health had shown a great interest in this project and had notified all Regional Hospital Boards of its existence.

Exhibitions.—The Council had participated during the year in an exhibition at the Royal Society of Health and in one at the British Medical Association Meetings; the subject of the exhibit was "The Prophylaxis of Rheumatic Fever", and it was prepared by Professor Bywaters at the Canadian Red Cross Memorial Hospital, Taplow.

Grants.—The Heberden Society, which existed for the advancement of the study of the rheumatic diseases, had continued to be supported by the Council, and had held regular meetings, lectures, and demonstrations.

The Council also continued its grants to the libraries of the B.M.A. and R.S.M. for the purchase of books on rheumatism and arthritis. *The Annals of the Rheumatic Diseases*, founded by the Council and published by the B.M.A., continued to report the Council's activities. The journal was recognized as the leading publication for scientific papers on rheumatic disorders.

COMMONWEALTH

Australia

Australian Rheumatism Council.—Progress had been made in the organization of specialists interested in the diagnosis and treatment of the rheumatic diseases, in the training of staff of clinics at the various public hospitals, and in the dissemination of information to the profession and general public.

This was largely the work of individual professional members of the Council acting in various capacities as members of the teaching staffs of the universities and hospitals, of medical post-graduate committees, and of the British Medical Association, and through liaison with press and radio stations.

Pan-Pacific Rehabilitation Conference.—A regional conference on Rehabilitation was held in Sydney in November, 1958, under the auspices of the International Society for the Welfare of Cripples. Over 1,000 delegates attended, including visitors from the United Kingdom, U.S.A., New Zealand, Greece, Thailand, South Vietnam, Korea, and Australia. The medical director, Dr. Nelson, acted as moderator of a session entitled "Rheumatism", the speakers being Dr. G. A. Q. Lennane (*New Zealand*), Dr. Leigh Wedlick (*Melbourne*), and Mrs. M. M. Kegel, occupational therapist (*Sydney*). A paper on "The Value of Active Splinting as a Rehabilitation Measure" was read by Dr. Michael Kelly (*Melbourne*).

Australian Rheumatism Association.—The Australian Rheumatism Association had continued to act in the same relationship to the Australian Rheumatism Council as the Heberden Society to the Empire Rheumatism Council.

The annual meeting of the Australian Rheumatism Association arranged to coincide with the week of the Pan-Pacific Rehabilitation Conference, was held at the Royal Prince Alfred Hospital on November 15. The programme included clinical case presentations by Drs. Harding Burns, Peter Harvey, and Selwyn Nelson, and a paper on "Gout in Maoris" by Dr. G. A. Q. Lennane (*New Zealand*).

The week-end course in rheumatic diseases was held in Sydney in October, under the auspices of the Post-graduate committee in medicine in the University of Sydney, under the supervision of Dr. Ralph Reader.

Post-graduate instruction of a similar nature was included in courses arranged in other states by the appropriate post-graduate committees.

Special instruction in the diagnosis and treatment of the rheumatic diseases was also included in the Annual Revision Course conducted by the post-graduate committee in medicine in the University of Sydney, and in various diploma courses.

Dr. Kitchener Smith had spent 6 months in the United Kingdom and U.S.A. studying rheumatic diseases.

Medical Research.—Medical members of the council had conducted clinical trials of new steroid preparations. Preliminary reports on the new 16-methyl-9-alpha-fluoroprednisolone were made at the annual meeting of the Australian Medical Association.

A legacy from the late Dr. L. T. A. Parr, M.P., of £1,000, had been invested for the purpose of establishing a triennial prize for research in the rheumatic diseases.

An offer from Roussel Laboratories Ltd., London, to create a Fellowship, tenable at Royal Prince Alfred Hospital and Sydney University, for research in collagen and rheumatic diseases had been accepted by the Royal Prince Alfred Hospital.

New Zealand.—A year of activity was also reported from the New Zealand Rheumatism Association. At the Annual General Meeting, held in Wellington on October 31 and November 1, 1958, clinical papers were presented by members.

Ann. Rheum. Dis. (1959), **18**, 145.

HEBERDEN SOCIETY

Clinical Meeting.—The Society met on February 27, 1959, at the London Hospital. The President, Prof. J. H. Kellgren (*Manchester*), welcomed Dr. Peter Heberden of Johannesburg, South Africa, a direct descendant of the Society's patron.

DR. R. M. MASON (*London*) presented three cases.

(1) The first patient was first seen in 1953 at the age of 22, complaining of painful feet which had caused him to be invalided out of the Royal Marines. The condition had been diagnosed as gout. The patient said that his feet had been painful since the age of 14, and 2 years previously he had had gonorrhoea with an associated Achilles bursitis.

There was arthritis of the terminal interphalangeal joints of both big toes and tenderness of the left fourth metatarsophalangeal joint, but no other peripheral or spinal arthropathy.

The erythrocyte sedimentation rate was 5 mm./hr, the Rose test was negative, and plasma uric acid estimates were 7·6, 6·4, 5·9, and 5·5 mg. per cent. *X* rays of the feet showed erosions of the terminal interphalangeal joints of both big toes and a destructive arthritis in the left fourth metatarsophalangeal joint. The sacro-iliac joints were normal.

He was treated with phenylbutazone with a fairly satisfactory response. Later *x* rays showed some healing of the right first terminal interphalangeal joint and some deterioration of the left fourth metatarsophalangeal joint.

The possibility of Reiter's disease was considered in view of his previous history. It was not possible to massage any pus from the prostate (4 cells per one-twelfth field), but there was one thread containing pus cells in the early morning specimen. The patient had since been lost sight of and the diagnosis remained uncertain.

(2) The second patient, referred by Mr. Osmond-Clarke, was a man aged 29 who complained of chronic low backache disturbing his sleep in the early hours; he gave a history of an acute arthritis of the wrists and ankles and a plantar fasciitis which had developed at the age of 19 whilst he was in the Navy. He had been invalided with a small pension. Later he had acute low backache, suggestive of a disk lesion. There was no history of genito-urinary infection.

The lumbar spine was moderately limited in lateral flexion. He was able to flex to a handsbreadth below the knees. The chest expansion was $1\frac{3}{4}$ inches. There was no evidence of a peripheral arthropathy.

The erythrocyte sedimentation rate was 20 mm./hr (Westergren). *X* rays showed bilateral sacro-iliitis. The lumbar spine appeared normal.

A diagnosis of ankylosing spondylitis was made and the patient was treated with phenylbutazone, to which he made the usual satisfactory response to such an extent that he asked if his brother (Case 3), a London taxi-driver, could also be seen.

(3) The third patient, a man aged 30, had had at the age of 15 an attack of arthritis of the hands and feet. At first the feet were worse affected than the hands. Subsequently he developed a polyarthritis of most peripheral joints. He was in and out of hospital for 4 years, and was treated by splinting, physiotherapy, gold and tonsillectomy. At the age of 25 he had had an attack of iritis in the right eye. At the age of 28, *i.e.* 13 years after the onset, he had had deep *x*-ray therapy which gave some relief.

He still complained of low backache and painful feet, his sleep being disturbed by morning stiffness. There was some discomfort of the right hand on overuse. The lumbar spine was rigid, and the dorsal spine showed a few degrees of rotation only. The chest expansion was 1 inch. The ischial tuberosities and symphysis pubis were tender. Both shoulders were slightly limited.

The erythrocyte sedimentation rate was 45 mm./hr (Westergren). The Rose test was negative. *X* rays showed bilateral sacro-iliitis. There was calcification of the lumbar spine with squaring of the vertebrae, and severe arthritis of metacarpophalangeal joints with marked destructive changes, but without osteoporosis.

A diagnosis of ankylosing spondylitis was made as in Case 2.

Comment.—There were four siblings altogether in this family: Cases 2 and 3, a girl aged 25, and a boy aged 15, who had painful heels but had not been examined. On further questioning, however, it was admitted that there was also a cousin with arthritis, and this proved to be Case 1, the fathers of the two families having been brothers. It was suggested, therefore, that Case 1 might also have ankylosing spondylitis, so far affecting only the peripheral joints.

Discussion: PROF. KELLGREN asked if the metatarsophalangeal joints in the first case were ankylosed.

MR. A. J. KING (*London*) asked if the second and third cases had been investigated for genital infection.

DR. MASON replied that the joints in question were ankylosed and that the two cases had not been investigated for genital infection, or for gonorrhoea in particular, as it had not seemed tactful to do so!

Uveitis, Arthritis, and Non-Specific Genital Infection. By DR. R. D. CATTERALL (*London, introduced*): 222 male patients (who had attended for the first time at the Institute of Ophthalmology and were referred for uveitis) were examined in detail for evidence of arthritis and genital infection. 142 (64 per cent.) were found to have

chronic prostatitis (defined as the presence of more than ten white cells per field in several one-twelfth high-power fields, or of clumps of pus, in the microscopy of the prostatic fluid); 150 had anterior uveitis, and 108 (72 per cent.) of these were found to have chronic prostatitis; 26 had generalized uveitis and chronic prostatitis occurred in eighteen (69 per cent.); 28 had posterior uveitis and only nine (32 per cent.) had chronic prostatitis. Eighteen of the patients examined did not have uveitis and chronic prostatitis occurred in seven (39 per cent.). If only cases with anterior or generalized uveitis were considered, the incidence of prostatitis was about 70 per cent. In contrast, the incidence in 44 in-patient controls of the same age groups admitted to the surgical wards was 29 per cent.

Reiter's disease was diagnosed in 52 cases (23 per cent.), ankylosing spondylitis in 29 (13 per cent.), atypical sacro-iliitis in fourteen (6 per cent.), and plantar fasciitis in seven (3 per cent.). A syndrome of symptomless sacro-iliitis, chronic prostatitis, and isolated or recurrent attacks of uveitis was seen in six patients.

Detailed bacteriological, haematological, and serological investigations failed to reveal a likely causative organism.

Dr. Catterall suggested that Reiter's disease, ankylosing spondylitis, atypical sacro-iliitis, and plantar fasciitis might be manifestations of one disease, which might be caused by genital infection, and of which anterior uveitis was a common component.

Discussion: PROF. E. G. L. BYWATERS (*Taplow*) felt that the crux was the definition of chronic prostatitis. He would be interested to know what was the natural distribution of prostatitis *as defined by Dr. Catterall*. What was the incidence in babies, for example, or in the schoolboys and virginal males who were liable to ankylosing spondylitis?

MR. A. J. KING (*London*) said that evidence in regard to infants and school children would be very difficult to obtain. He felt that Dr. Catterall's criteria represented a definite and quite gross evidence of chronic prostatitis and he himself was inclined to regard as abnormal the presence of even two or three pus cells per high-power field. Studies on presumed normal males had shown an incidence of prostatitis of from 15 to 30 per cent.; the figure of 72 per cent. in association with anterior uveitis must be considered significant.

PROF. KELLGREN suggested that the uveitis and the finding of leucocytes in prostatic fluid might both be manifestations of an underlying disease.

MR. A. J. KING agreed that what was cause and what was effect had not been proved by the finding of the association. Until a specific organism was found, the theory of prostatic infection could not be proved. Nevertheless, the association could not be disregarded.

DR. A. ST. J. DIXON (*London*) wondered whether there was any evidence of increased incidence of uveitis in paraplegic patients who were a group also liable to chronic prostatitis and sacro-iliitis.

DR. J. SHARP (*Manchester*) asked what percentage had the chronic spondylitis of Reiter's disease?

MR. KING said that an answer could not be given to these questions at present.

DR. W. S. C. COPEMAN (*London*) asked whether any clinical or statistical information was available on the significance of urogenital infections in women in relation to uveitis.

DR. CATTERALL replied that a study of the condition in women was being undertaken. It was more difficult to assess chronic genito-urinary infection in women than in men.

DR. SHARP asked about differentiation between granulomatous and non-granulomatous uveitis. He agreed with Dr. Catterall that anterior uveitis was the type especially associated with arthritis, but on further subdividing anterior uveitis it was only the non-granulomatous variety which was associated with arthritis.

DR. CATTERALL agreed that the majority had the non-granulomatous type.

Treatment of Rheumatoid Arthritis by a Sanatorium Regime (The Black Notley Experiment). By DR. W. G. WENLEY (*London, introduced*): This paper and the discussion thereon appears on p. 91 of this issue of the *Annals*.

The Kidney in Gout. By DR. D. GREENBAUM (*London, introduced*): It was generally accepted that the incidence of renal disease in patients with gout had increased. There was still speculation about the mechanisms involved, partly because the end stages of most types of renal disease tended to look the same. In an attempt to resolve this particular difficulty renal biopsy, supplemented by fairly comprehensive renal function tests, had been used in thirteen patients with gout. Of these, three were suffering from obvious renal disease with uraemia; their renal biopsies showed much interstitial fibrosis, loss of tubules, and cellular infiltration (one of them may have had a coincidental glomero-nephritis). Of the remaining ten patients, eight had moderately abnormal renal function tests (diminished power to excrete phenolsulphphthalein or to concentrate urea), and eight had a slightly abnormal renal biopsy picture. This consisted of a variable increase in the interstitial fibrous tissue, other components of the kidney appearing normal. In spite of special techniques, uric acid or urates could not be demonstrated in any of the biopsy specimens. Appreciable quantities of uric acid were found in only two of a further eight kidneys from gouty patients examined *post mortem*, seven of which were histologically abnormal.

The abnormalities found in the renal biopsy material were not specific, either in the kidneys showing gross changes or in those showing minor interstitial fibrosis. Renal biopsy in these patients had not thrown any further light on the aetiology of renal damage in gout, although it was notable that completely normal kidneys, as shown by both histological appearance and function tests, could not be demonstrated in any of the patients.

Comparison of the Rose-Waaler and Latex-Fixation Tests. By DR. V. L. STEINBERG (*London, introduced*): The Rose-Waaler and latex-fixation tests for rheumatoid arthritis had been performed in parallel on 504 patients. The Ball (1950) modification of the Rose-Waaler test was employed, and agglutination by a serum dilution of 1 in 16 was taken as positive. The original method of Singer and Plotz (1956) was employed for the latex

test, except that refrigeration and centrifuging of the tubes was found to be of no advantage and was not used. In 259 patients suffering from rheumatoid arthritis as defined by the American Rheumatism Association (Ropes, 1956), both tests were positive in 153 (59 per cent.), the Rose test positive and the latex test negative in fifteen, the latex test positive and the Rose test negative in ten, and both tests negative in 81. There was agreement between the two tests in 234 sera (90 per cent.). In all, 168 Rose tests were positive (65 per cent.) and 163 latex tests were positive (63 per cent.). Altogether 178 (69 per cent.) of patients were sero-positive.

In 245 patients with miscellaneous conditions, both tests were negative in 230, the Rose test positive and the latex test negative in five, the latex test positive and the Rose test negative in six, and both tests positive in four. There was agreement between the two tests in 468 cases (93 per cent.).

When both tests were positive the middle to high Rose titres tended to be associated with high latex-fixation titres. It was not possible, however, to predict the titre of one test from the titre of the other. If both tests were performed together, this would result in a slightly higher total positive serology, but the advantage was quite out of proportion to the work involved. The latex-fixation test was the less time-consuming, and even in the lower dilutions the end-point was easy to define. It was therefore preferable for routine work.

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Ropes, M. W., Bennet, G. A., Cobb, S., Jacox, R., and Jessar, R. A. (1956). *Bull. rheum. Dis.*, **7**, 121.
Singer, J. M., and Plotz, C. M. (1956). *Amer. J. Med.*, **21**, 888.

Discussion: DR. H. LOEWENTHAL (*Enfield*) said that he had compared the Rose and latex-fixation tests and that his results confirmed those of Dr. Steinberg. He had had to use a latex of British origin which had proved quite satisfactory.

PROF. KELLGREN asked whether Dr. Steinberg had any information about the distribution of subcutaneous nodules in these cases, and also how many patients were African and how many had liver disease.

DR. STEINBERG replied that the proportion of positive tests was higher in patients with nodules. None had liver disease and no Africans were included in the series.

DR. A. ST. J. DIXON said that at Hammersmith it had been found that the latex test correlated less well with nodules than the Rose test.

Tendon Lesions in the Rheumatoid Hand. By MR. O. J. VAUGHAN-JACKSON (*London, introduced*): In 1946 it had been found that tendon attrition on the lower end of an ulna roughened by rheumatoid arthritis had caused abrupt painless rupture of the extensor communis tendons. This had led in turn to the recognition that the lesion was exceedingly common despite the absence of reference to it in the literature before that date. It was a common cause of flexion deformities at the metacarpophalangeal joints, and if discovered early enough, before the deformity became fixed, the lesion was reparable. The clinical picture was monotonously uniform. The little finger tendon was usually the first to go (or sometimes that of the ring finger), and the other tendons then ruptured *seriatim*—ring, middle, index—in that order. Prompt exploration always revealed the abrasive spicule, though it was sometimes hidden by pouting synovial tissue or a valvular arrangement of tissue over it. There was always a hole in the floor of the dorsal tendon compartment over the lower end of the ulna, through which the spicule abraded the tendon. At later explorations the tendon ends were seen to be joined by a thin strand which resembled a stretched tendon, but dissection always revealed the separated tendon ends. At earlier explorations this strand was seen to be, quite unmistakably, the tube of paratenon within which the tendon ends had retracted. Timely removal of the lower end of the ulna and repair of the tendons by transfers or free grafts restored normal function. Similar attrition ruptures of flexor tendons in the carpal tunnel or in the digital sheaths, and of extensor tendons over the lower end of radius, were steadily coming to light, and it was quite clear that the usual attitude to deformity in the rheumatoid hand should be revised, since the evidence discovered at operation consistently upset prevailing notions about tendons in rheumatoid arthritis. Tendon ruptures were a far more important factor in deformity than had hitherto been recognized, but they enjoyed the unusual distinction among rheumatoid lesions of being reparable.

Discussion: DR. J. J. R. DUTHIE (*Edinburgh*) said that he had had a letter from an American writer who had seen six such cases in the last 9 months and wondered whether they were associated with steroid therapy. The implication was that so many American patients were now on steroid therapy that the incidence of the complication in untreated patients had to be sought in Britain.

MR. VAUGHAN-JACKSON replied that in some, at least, of the early cases the patients had not been given steroids at all. The macroscopic condition of the tendon showed nothing to suggest that there was anything abnormal. It seemed to him that the attrition by itself was a sufficient explanation.

PROF. E. G. L. BYWATERS asked how long after the rupture repair could be attempted.

MR. VAUGHAN-JACKSON replied that repair could be attempted at any time provided that the joints were still capable of being moved. If the fingers had dropped too long, the flexors were adaptively shortened and the relatively immobile joints were specially vulnerable to the rheumatoid process. Once a physical deformity had developed, the operation would do no good unless it was accompanied by some form of arthroplasty.

Centenary of the Devonshire Royal Hospital, Buxton

A joint meeting of the Heberden Society and British Association of Physical Medicine is to be held on July 25 and 26, 1959. Members of the Canadian Rheumatism Association, the Canadian Association of Physical Medicine, the Nederlandse Vereniging van Reumatologen, and Manchester Regional Orthopaedic Association are invited to participate.

Anyone wishing to attend or to submit a communication should apply to the Organizing Secretary, Dr. W. S. Stoddart, 35, Ballbrook Court, Wilmslow Road, Manchester, 20.

Ann. rheum. Dis. (1959), **18**, 148.

B.M.A. JOINT ANNUAL MEETING WITH C.M.A.

Edinburgh, July 18-24, 1959

The following meetings and demonstrations of interest to rheumatologists will form part of the British and Canadian Joint Annual Meeting.

Round-Table Conferences

JULY 22, AT 9 A.M.

"Rheumatic Heart Disease in Pregnancy."

Chairman: Prof. G. Maughan (*Montreal*)
Speakers: Dr. Leslie Watt (*Toronto*)
Dr. W. Greenwood (*Toronto*)
Mr. G. H. Wooler (*Leeds*)
Dr. W. Whitaker (*Leeds*)

JULY 23, AT 9 A.M.

"Rheumatic Diseases."

Chairman: Dr. A. W. Bagnall (*Vancouver*)
Speakers: Dr. D. C. Graham (*Toronto*)
Dr. J. J. R. Duthie (*Edinburgh*)
Prof. E. G. L. Bywaters (*London*)
Dr. W. S. Tegner (*London*)

Section of Rheumatic Diseases

JULY 23, AT 2.30 P.M.

Joint Presidents: Dr. A. W. Bagnall (*Vancouver*)
Dr. G. D. Kersley (*Bath*)
Joint Vice-Presidents: Dr. D. C. Graham (*Toronto*)
Dr. J. J. R. Duthie (*Edinburgh*)
Hon. Secretaries: Dr. J. H. H. Glyn (*London*)
Dr. R. J. G. Sinclair (*Edinburgh*)

SYMPOSIUM: "The Polyarthritic Syndrome"

Chairman: Dr. W. S. C. Copeman (*London*)
Speakers: Prof. E. G. L. Bywaters (*London*), "Acute Polyarthritis"
Prof. J. H. Kellgren (*Manchester*), "Chronic Polyarthritis"
Dr. D. C. Graham (*Toronto*), "Spondylitis"
Dr. S. Dworkin (*Montreal*), "Soft-tissue Rheumatism"

SHORT PAPERS

Chairman: Dr. J. R. L. Woodbury (*Halifax, Nova Scotia*)
Dr. J. S. Crawford (*Toronto*), "Principles of Rehabilitation for the Arthritic Patient"
Dr. F. P. Dewar (*Toronto*), "The Problem of Painful Feet"
Dr. R. J. G. Sinclair (*Edinburgh*), "Diagnostic Problems in a Rheumatism Clinic"
Dr. G. D. Kersley (*Bath*), "Current Views on Gout and its Treatment"
Dr. A. G. S. Hill (*Stoke Mandeville*), "Laboratory Tests and Prognosis in Rheumatoid Arthritis"

PANEL DISCUSSION: "Drugs in the Treatment of Rheumatic Disease"

Chairman: Dr. A. W. Bagnall (*Vancouver*)
Speakers: Dr. J. N. Swanson (*Toronto*)
Prof. F. S. Brien (*London, Ontario*)
Prof. R. E. Tunbridge (*Leeds*)
Dr. F. Dudley Hart (*London*)

Colour Television

JULY 20, AT 1.30 P.M.

Dr. J. J. R. Duthie (*Edinburgh*), "Prevention and Correction of Deformities in Rheumatoid Arthritis"

Scientific Exhibition

EMPIRE RHEUMATISM COUNCIL

"Quiz on Early Radiological Signs in Rheumatoid Arthritis"
"Course and Prognosis in Rheumatoid Arthritis"
"What is the 'Epidemiology' of Rheumatic Diseases?"

GLASGOW ROYAL INFIRMARY

"The Synovial Fluid in Arthritis"

CANADIAN RHEUMATISM ASSOCIATION

Officers, 1958-59

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ARGENTINE LEAGUE AGAINST RHEUMATISM

LIGA ARGENTINA CONTRA EL REUMATISMO

The president of the Argentine League against Rheumatism, Dr. S. Tarnopolsky, has been made honorary professor of the faculty of medicine in the University of La Paz.

Ann. rheum. Dis. (1959), **18**, 149.

EUROPEAN LEAGUE AGAINST RHEUMATISM

Officers

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IV EUROPEAN CONGRESS OF RHEUMATOLOGY

Istanbul, 1959

The IV European Congress of Rheumatology is being organized by the Association for Rheumatism Research and Treatment in Turkey, and will be held at Istanbul on September 28-30, 1959. All enquiries and correspondence should be addressed to the Secretary-General:

Prof. Dr. Hami Koçaş,
Tip Fakültesi,
Fiziktedavi Enstitüsü,
Ankara, Turkey.

COMMITTEE FOR THE CONGRESS

Chairman: Prof. Dr. Nüzhet Şakir Dirisu
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Officers, 1959

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NEW YORK RHEUMATISM ASSOCIATION

At the Annual Meeting of the New York Rheumatism Association held on April 14, 1959, at New York University-Bellevue Medical Center, the following officers were elected:

President: Dr. James A. Coss, Jr.
Vice-President: Dr. Harry Bartfeld
Secretary-Treasurer: Dr. Albert W. Grokoest, 622 West 168th Street, New York 32, N.Y.

Ann. rheum. Dis. (1959), **18**, 150.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi *of steroid therapy.*

Acute Rheumatism

Frequency and Diagnostic Importance of So-called Minor Clinical Manifestations of Rheumatic Fever in Childhood. (Frequenza ed importanza diagnostica delle manifestazioni cliniche cosidette "minori" nella malattia reumatica dell'infanzia.) FRANCESCO, R., and SERGIO, M. (1958). *Clin. pediat.*, **62**, 105. Bibl.

A statistical analysis is presented of the clinical features of the primary attack of rheumatic fever as seen in 206 consecutive cases admitted to the Paediatric Clinic of the University of Florence during the period 1947-57, particular reference being made to the incidence of atypical or "minor" manifestations. The incidence of the disease was highest (157 cases) between the ages of 6 and 11 years, while the seasonal incidence was highest from September to November and lowest in August. In 157 of the 206 cases, the clinical picture was typical, with involvement of the joints (during the first week in 134 cases and between the 2nd and 4th weeks in 23). In the remaining 49 cases (23·78 per cent.), the onset was marked by atypical symptoms involving the digestive or respiratory tract or the nervous system, making an accurate and early diagnosis difficult. In 22 of these 49 cases the patient complained of severe abdominal pain suggesting an acute surgical condition and in eight the clinical picture resembled pneumonia, bronchopneumonia, or pleurisy. In 21 cases the only symptom was a rise in temperature, sometimes associated with a sore throat.

The authors are of the opinion that tonsillectomy is of no real value in the prophylaxis of rheumatic fever and may even precipitate an attack. In 21 of their cases rheumatic fever developed despite the fact that the tonsils had been removed, and in four of these cases the operation had been performed within 15 to 30 days of the onset of the attack. In view of the high incidence of atypical forms of acute rheumatism they recommend the institution of "precautionary" treatment with anti-rheumatic drugs and antibiotics in all cases in children of indeterminate febrile illness which might be of rheumatic aetiology. *Franz Heimann.*

Evaluation of Hormonal Therapy in Rheumatic Fever. ROBLES GIL, J. (1958). *Arch. interamer. Rheum.*, **1**, 441. 7 figs, 40 refs.

In this paper from the Rheumatology Department of the National Institute of Cardiology, Mexico, the author analyses in some detail the results obtained with hormones (corticotrophin (ACTH), cortisone, or prednisone) in 66 patients with rheumatic fever. There was "clear improvement" in the signs and symptoms, but the effect of the hormones on the duration of rheumatic activity was problematical. The author briefly discusses a series of thirty patients with rheumatic fever who were treated with salicylates, and concludes that they did less well than patients given hormonal treatment. A study of the clinical records of 500 untreated patients left no doubt that progress in these patients was less favourable than in those given either hormones or salicylates.

K. C. Robinson.

Clinical Features of the Course of Acute Rheumatism in Children at the Present Time. ÈDEL'MAN, Z. I. (1958). *Pediatrija*, **36**, No. 12, 7. 3 figs, 4 refs.

Comparison of the findings in 1,711 cases of acute rheumatism in children admitted to the Rheumatic Clinic of the Paediatric Institute and First Children's Hospital of the Ministry of Health of the R.S.F.S.R. during the past 8 years with those in cases admitted during a previous period (1934-49) shows that certain changes have taken place in morbidity, clinical course, and mortality in the different age groups. Thus, of the children admitted during the more recent period, 63·6 per cent. were suffering from their first attack of rheumatism compared with 53 to 54 per cent. in the earlier period. There was also an increase in morbidity among children under 8 years, who accounted for 38 per cent. of admissions compared with 18 to 20 per cent. previously, while the proportion aged 2 to 5 increased from 3·8 to 10·9 per cent. The polyarthritic form of the disease was generally milder, and its incidence decreased from 75 to 28·8 per cent. The incidence of cardiac involvement in such cases, however, increased from 11 to 60·7 per cent., though the

carditis tended to be milder and pancarditis and multiple valvular involvement were less common. In view of the increasing frequency of rheumatic carditis without joint symptoms the need for accurate diagnosis is stressed. The incidence and severity of chorea increased during the immediate post-war period, but have now diminished again, though the possibility that some cases are being diverted to neurological units is envisaged. Certain other rheumatic manifestations, such as nodules, erythema annulare, and pleurisy, were less common than previously, but the incidence of other pulmonary complications and of renal and abdominal involvement showed no change.

Although acute rheumatism has generally become more benign in recent years and the mortality from first attacks in the present series was only 0·43 per cent., the mortality among older children, including many with chronic and recurrent disease, remains disturbingly high. Out of 65 children dying during the past 6 years at the First Children's Hospital from acute rheumatism, 36 were over 12 and five over 14 years old. In the whole series of 1,711 cases the mortality among children over 12 was 6·7 per cent., which is little better than the corresponding figure of 7·4 per cent. for the earlier period, while the death rate in repeat attacks (all age groups), though much lower than in pre-war years, was 5·5 per cent. In older children the disease now tends more frequently than hitherto to take a severe, relapsing course, 13 per cent. of all cases in children over 12 years old being of this type.

The improvement in certain features of the disease is attributed to improved social conditions, better hospital facilities, and the use of amidopyrine, phenylbutazone, and hormone preparations in treatment. The need for specialized sanatoria for the treatment of severe chronic cases and of special schools for children with the milder forms of rheumatism is stressed, while the importance of accurate assessment of cardiac lesions with a view to operation is emphasized. *Margot G. Dunlop.*

Changes in Certain Serum Enzymes (Oxalacetic and Pyruvic Transaminase, Lactic Dehydrogenase, and Cholinesterase) in Rheumatic Fever. (Comportamento du alcuni enzimi (transaminasi ossalacetica e piruvica, latticodeidrogenasi, colinesterasi del siero) nella malattia reumatica.) CATTANEO, R., PELOCCHINO, A. M., PRINOTTI, C., and RIGAZIO, G. (1958). *Reumatismo*, **10**, 366.

The study of the enzymes of the blood has recently been recognized to be of considerable value in the diagnosis and prognosis of various diseases. Thus characteristic changes in the oxalacetic transaminase activity of the serum occur in myocardial infarction, in pyruvic transaminase activity in viral hepatitis, and in acid-phosphatase activity in cancer of the prostate. The transaminases are normally present in striated muscle, the liver, the myocardium, and the kidney, and the amount present in the blood increases immediately when one of these organs is damaged, as in cases of myocardial infarction or viral hepatitis; the level is also found to be increased in certain cases of neoplasm, in myopathies, and in a number of other diseases in which the activity of other enzymes shows no significant change. The activity of lactic dehydrogenase in the serum is also found to be elevated in cases of neoplasm, myocardial infarction, and acute hepatitis, whereas serum cholinesterase activity is diminished in these diseases and in numerous other conditions.

At the Medical Clinic of the University of Turin the authors have studied the serum enzyme levels in seventeen male and eight female patients aged 7 to 64 years with rheumatic diseases. They included six cases of rheumatic fever with carditis, eight cases of rheumatic carditis without active articular involvement, five cases of acute articular rheumatism, two cases of Henoch's purpura (one with carditis), and four cases of rheumatoid arthritis. The serum oxalacetic transaminase and lactic dehydrogenase levels were frequently increased, but no changes were observed in the serum pyruvic transaminase and cholinesterase levels. It was found that increased serum enzyme activity was related to the presence of cardiac involvement and not to the activity of the rheumatic process in the absence of carditis. *E. Forrai.*

Lesions of Rheumatic Fever in Patients treated with Cortisone. III. The General Response of the Organism. Discussion and Conclusions. (Las lesiones de la fiebre reumatica en los enfermos tratados con cortisona. III. La repuesta general del organismo. Discusion general y conclusiones.) COSTERO, I., BARROSO-MOGUEL, R., CHÉVEZ, A., MONROY, G., and CONTRERAS, R. (1958). *Arch. Inst. Cardiol. Méx.*, **28**, 427. 14 figs, 37 refs.

The treatment of acute rheumatic carditis with corticosteroids produces no changes in old scars, but new lesions are rich in cells and poor in collagen. Fibroblasts develop in the media of the cardiac vessels and in the connective tissue of other organs, especially the gonads in children. The vegetations contain much Schiff-positive material and remain unorganized for a long time. The Aschoff nodes develop basophilic cells and bipolar fibroblasts.

Corticosteroid treatment does not reduce the incidence of any of the usual complications of rheumatic fever other than arthritis and encephalitis. Indeed, among thirty cases examined *post mortem* by the authors at the National Institute of Cardiology of Mexico, centrilobular hepatic necrosis due to cardiac insufficiency occurred more often in severe cases treated with cortisone than in untreated severe cases. Cushing's syndrome, adrenal cortical atrophy, acute peptic ulceration, and atypical infections were all observed as complications of corticosteroid therapy. *M. Lubran.*

Sydenham's Chorea. LESSOF, M. (1958). *Guy's Hosp. Rep.*, **107**, 185. 7 figs, 44 refs.

The author reviews the literature and presents an analysis of 210 attacks of chorea seen during a period of 8 years at the Canadian Red Cross Memorial Hospital, Taplow, Bucks, in 175 patients, of whom 148 had single attacks, 22 had two attacks, three had three, one had four, and one had five. In discussing sex incidence, the

author points out that, of 1,000 patients admitted to the hospital with rheumatic fever (including 209 with chorea), 511 were female and 489 male, whereas of the 209 with chorea, 133 were girls and 76 boys. The age ranged from 3 to over 22 years, the maximum incidence being in the age group 6 to 14 years. Of nineteen patients with chorea over the age of 15, only one was a male. The series included three cases of chorea gravidarum. Among the 36 most severe cases, the sex difference was still more marked, thirty of these patients being female. The duration of the chorea varied; excluding four patients who died of carditis while still choreic and one who died of chorea and hyperpyrexia, about half the patients recovered in 10 weeks, many recovered in less than a week, while in others symptoms persisted for a year or more.

As regards the association of chorea with rheumatic fever, the modified Duckett Jones criteria for the diagnosis of rheumatic fever were satisfied in 117 of the cases. Arthritis was observed in 36·8 per cent. of first attacks and in 15 per cent. of subsequent attacks. Carditis occurred in 72·8 per cent. of first and in 67·1 per cent. of subsequent attacks. The corresponding figures for rheumatic nodules were 21·3 and 11·0 per cent., and for erythema marginatum 6·7 and 6·8 per cent. respectively. Two of the patients had systemic lupus erythematosus. In those with arthritis or joint pains there was usually a delay of from 4 to 24 weeks or more between the onset of joint symptoms and the development of chorea, and in only six out of 63 cases did chorea precede the joint symptoms. In fourteen cases of rheumatic fever chorea developed after the erythrocyte sedimentation rate had returned to normal. There was no significant difference between the incidence of different types of heart murmur in acute rheumatic fever and in chorea. Of 131 patients who had carditis with chorea, 102 had a basal aortic diastolic murmur, 95 a mitral diastolic murmur, 42 a mitral pansystolic murmur, and ten a presystolic murmur. Less than 20 per cent. of the patients seen at a follow-up clinic had a recurrence while under observation, but out of 166 so followed, 46 continued to have chorea-like movements, usually when they were tired or excited, for an average of 11 months after the chorea had disappeared. In two of the fatal cases studied *post mortem* no clear-cut abnormalities could be demonstrated in the central nervous system. The pathology and treatment of chorea are discussed. *C. Bruce Perry.*

Lesions of Rheumatic Fever in Patients treated with Cortisone. I. Special Consideration of Endomyocarditis. (Las lesiones de la fiebre reumática en los enfermos tratados con cortisona. I. Consideración especial de la endomiocarditis.) COSTERO, I., BARROSO-MOGUEL, R., CHÉVEZ, A., MONROY, G., and CONTRERAS, R. (1958). *Arch. Inst. Cardiol. Méx.*, **28**, 155. 19 figs.

This report (the first of three) from the National Institute of Cardiology, Mexico City, describes the necropsy findings with particular reference to the cardiac lesions in 30 patients who died of rheumatic fever after treatment mainly with various compounds of cortisone. Vegetations on the cardiac valves were found in 24 (80 per cent.) of the cases. The principal histological differences between cortisone-treated patients and others were that the former showed:

(1) a decrease in the number of Aschoff bodies and an increase in the number of fibroblasts and amount of collagen and scar formation;
(2) slower organization of the fibrinoid substance of the vegetations, with a fibroblastic reaction in the adjacent tissues and absence of inflammatory cells;
(3) a lessened tendency to organization and resorption of areas of necrosis. *M. Lubran.*

Value of the Study of the Serum Perchlorate-soluble Seromucoids and Orosomucoid in the Management of Rheumatic Fever. (Intérêt de l'étude des séromucoïdes perchlorosolubles et de l'orosomucoïde dans la surveillance du rhumatisme articulaire aigu.) BISERTE, G., BRETON, A., HAVEZ, R., and FONTAINE, G. (1958). *Arch. franç. pédiat.*, **15**, 800. 5 figs, 31 refs.

Among the battery of tests employed for the diagnosis of acute rheumatic fever and for following its clinical course during and after hormone treatment one of the most valuable is the study of the serum glucoprotein level, and particularly of its acid fractions, the perchlorate-soluble seromucoids. In a study here reported from the Department of Paediatrics, University of Lille, of 23 cases of acute rheumatic fever the authors found that the serum mucoid level was invariably elevated in the presence of rheumatic activity, even in the rare cases in which the erythrocyte sedimentation rate was normal (as in heart failure). This elevation can be demonstrated either by chemical analysis or by paper electrophoresis at a *p*H of 3·9; the latter method is simple and easy to perform. During treatment the level of serum mucoids is the slowest to return to normal, and in the authors' experience it is unwise to stop treatment until normal levels are reached, since otherwise relapses are liable to follow. *John Lorber.*

Children with Rheumatic Fever in Minnesota. ROSENFIELD, A. B. (1958). *Amer. J. publ. Hlth*, **48**, 1596. 1 fig., 4 refs.

Rheumatic Fever. A Review of the Literature. DONOVAN, R. J. (1958). *Bull. Sch. Med. Maryland*, **43**, 75. Bibl.

Thirty Years of Juvenile Rheumatism. HUGHES, L. (1959). *Med. J. Aust.*, **1**, 7.

Epidemiology and Prophylaxis of Rheumatic Fever in Childhood. (Epidemiologie und Prophylaxe des akuten rheumatischen Fiebers im Kindesalter.) LORENZ, E. (1959). *Wien. med. Wschr.*, **109**, 147. 15 refs.

Studies of the Peripheral Vascular System in Children with Rheumatic Fever. (Kilka sprawdzianów stanu obwodowego układu naczyniowego u dzieci z chorobą reumatyczną.) CHRAPOWICKI, T., and PATZEROWA, T. (1958). *Pediat. pol.*, **33**, 1145. 8 refs.

Attempt to Assess Morphological Changes in the Peripheral Vessels in Children with Rheumatic Fever. (Próba określenia zmian morfologiczynych obwodowego układu naczyniowego u dzieci z chorobá reumatyczna.) CHRAPOWICKI, T., and PATZEROWA, T. (1958). *Pediat. pol.*, **33**, 1157. 3 refs.

Electrophoretic Study of Serum Proteins in Active Rheumatic Fever. (Estudo eletroforético das proteinas do soro na febre reumática ativa.) DÉCOURT, L. V., and COSSERMELLI, W. (1958). *Arch. interamer. Rheum.*, **1**, 53. 36 refs.

Studies of Rheumatic Fever and Its Treatment. (Études sur la maladie de Bouillaud et son traitement.) CHEVALLIER, M. J. (1958). *Bull. Soc. méd. Hôp. Paris*, **74**, 962. 17 refs.

Rheumatic Fever Prophylaxis with Benzathine Penicillin G in Wyoming. GIDDINGS, L. E., and YODER, F. D. (1959). *Rocky Mtn med. J.*, **56**, 37. 5 refs.

Effect of Penicillin in Rheumatic Fever and Valvular Heart Disease. (Efecto de la penicilina sobre la enfermedad reumatica aguda u las cardiopatias valvulares.) MORTIMER, E. A., JR., VAISMAN B., S., VIGNAU I., A., GUASCH L., J., SCHUSTER, C., A., RAKITA, L., KRAUSE, R. M., ROBERTS, R., and RAMMELKAMP, C. H., JR. (1959). *Rev. med. Chile*, **87**, 3. 7 figs, 24 refs.

Chronic Articular Rheumatism (Rheumatoid Arthritis)

Familial Occurrence of the Rheumatoid Factor. ZIFF, M., SCHMID, F. R., LEWIS, A. J., and TANNER, M. (1958). *Arthrit. and Rheum.*, **1**, 392. 1 fig., 24 refs.

Although possession of the rheumatoid factor in the serum has been shown to be a fairly specific attribute of patients with rheumatoid arthritis, false positive reactions occur in a small proportion of cases in both agglutination and agglutination-inhibition tests with sensitized sheep erythrocytes and in the latex fixation test. In view of the evidence for a familial tendency in rheumatoid arthritis the authors decided to study the incidence of such positive results among members of the families of patients with rheumatoid arthritis compared with that in non-rheumatic subjects. In this paper from New York University College of Medicine they record the result of tests on two groups of relatives of patients with rheumatoid arthritis. In the first group, consisting of 140 relatives (44 parents, 36 offspring, and 60 siblings) of 46 patients, the euglobin fraction of the serum was examined by the agglutination and agglutination-inhibition techniques (Ziff *et al.*, *Amer. J. Med.*, 1956, **20**, 500; *Abstr. Wld Med.*, 1956, **20**, 387) and similar tests were carried out on 140 control subjects, none of whom had a personal or family history suggesting rheumatoid arthritis. Of the relatives, sixteen had rheumatic symptoms and were excluded from the comparison with the control series. Of the remaining 124 asymptomatic relatives, 21 (16·9 per cent.) gave a positive haemagglutination-inhibition reaction compared with seven (5·0 per cent.) of the control subjects. In nineteen (41 per cent.) of the 46 families tested at least one member gave a positive result. There was no significant variation in the incidence of positive reactions with age or sex, but symptoms were more common in female relatives than in males. The second group consisted of 71 relatives of 32 patients, 24 of the families having also been members of the first group. Each was matched with a control subject of the same sex and, with ten exceptions, of the same age within 2 years and the capillary-tube latex fixation test of Tanner and Ziff (*Arthrit. and Rheum.*, 1958, **1**, 376) performed on both. Of the 67 asymptomatic relatives, eight (11·9 per cent.) gave a positive result compared with one (1·4 per cent.) of the 71 control subjects.

Although these findings indicate that a substance with the properties of the rheumatoid factor occurs significantly more frequently in the serum of the healthy siblings, parents, and offspring of patients with rheumatoid arthritis than among control subjects from non-rheumatic families, the authors do not suggest that the available evidence is sufficient to show that the rheumatoid factor itself is inherited, since the increased agglutinating activity demonstrated may result from an increase in concentration of some normally occurring agglutinating substance. *Harry Coke.*

Purification of a Rheumatoid Factor. HEIMER, R., FEDERICO, O. M., and FREYBERG, R. H. (1958). *Proc. Soc. exp. Biol. (N.Y.)*, **99**, 381. 17 refs.

The authors, working at the Cornell University Medical College, New York, isolated a macroglobulin from sera of individuals with rheumatoid arthritis which agglutinated sensitized sheep erythrocytes and fixed gamma globulin latex particle suspensions. Details of the complex methods of isolation and purification of this factor are given. Evidence was adduced that the preparation was homogeneous and a component of the rheumatoid factor. Calculations based on the specific activity of the isolated factor showed that it occurs in concentrations from 0·1 to 20 mg. per cent. in sera of individuals which agglutinated sensitized sheep erythrocytes.

G. W. Csonka.

Treatment of Rheumatoid Arthritis with Chloroquine. FULD, H., and HORWICH, L. (1958). *Brit. med. J.*, **2**, 1199. 13 refs.

The literature on the use of chloroquine in the management of rheumatoid arthritis is reviewed. Results in treatment and following up 39 patients from 3 months to 4 years are described. Complete remission of the disease process was obtained in 30 per cent. of cases, a major improvement occurred in 50 per cent., and insignificant or no benefit was noted in about 20 per cent. of the patients. The drug proved harmless and was well tolerated in larger doses than used by other authors. Relapses whilst on chloroquine were not observed in our series.

We recommend a regime of treatment consisting in bed rest, induced pyrexia, blood transfusions, and salicylates during the first 3 weeks of treatment, and tablets of chloroquine sulphate, 200 mg. three times a day throughout

the treatment or immediately after induced fever—this dose of chloroquine to be continued until a remission has been obtained, when the dose may be decreased to 400 mg. daily (equals 300 mg. base). The maintenance therapy may be required for 12 months or longer. [*Authors' summary.*]

Cortisone and Corticotropin in the Treatment of Rheumatoid Arthritis. COPEMAN, W. S. C. (1958). *Arch. interamer. Rheum.*, **1**, 261. 6 refs.

Our present views on steroid therapy may very briefly be stated as follows:

(1) The majority of cases of rheumatoid arthritis will respond in time to what one may call the classical or conventional methods of treatment, *i.e.* systematic rest, physiotherapy, splintage, salicylates, gold salts, etc. These methods have not yet been outmoded by the introduction of steroid therapy, which is additional.

(2) A certain proportion of cases do not, however, respond to such classical treatment. In these, when none of the well-recognized contra-indications to steroid therapy are present it can be used and can make the difference between crippledom and painless independence. For various reasons we now sometimes prefer ACTH to cortisone for this purpose, if biochemical control is available.

(3) When long-term treatment of this sort is to be embarked upon it must be agreed by the patient that he will remain under the regular supervision of the prescribing doctor, so that undesirable side-effects may be noted in their early and harmless stage. By periodical assessment the total dosage of the steroid substance may also be kept down to the therapeutic minimum consistent with clinical advantage, and this will avoid the danger of hypercortisonism. It is often convenient for the patient to learn to give his own injections.

(4) If used, not empirically but in the way described, and only in properly selected cases, the use of steroid therapy seems to have opened a completely new and hopeful era in the treatment of the rheumatic diseases.—[*Author's summary.*]

Clinical Studies of Seven Patients with Rheumatoid Arthritis and uniquely Large Amounts of Rheumatoid Factor. FRANKLIN, E. C., KUNKEL, H. G., and WARD, J. R. (1958). *Arthrit. and Rheum.*, **1**, 400. 3 figs, 16 refs.

The rheumatoid factor, which is present in the serum in most cases of rheumatoid arthritis, is known to be associated with a component of γ globulin of high molecular weight and to exist in the serum as a complex with a sedimentation constant of approximately 225 which can be detected by direct ultracentrifugal examination. Sera from 151 patients with rheumatoid arthritis (96 out-patients selected at random at the Massachusetts General Hospital and 55 patients referred to the Rockefeller Institute, New York, because of very severe disease refractory to treatment) were examined by various serological tests, and those sera showing the highest titres of rheumatoid factor were further examined in the ultracentrifuge.

Sera from one of the former and six of the latter group contained more than 50 mg. of 22-S material per 100 ml. and these patients were selected for further study. All seven proved to have advanced arthritis of Stage III or IV and of 5 to 15 years' duration. Comparison of the incidence of various clinical features among these patients with that among the group of 96 selected at random showed a much more frequent occurrence of subcutaneous nodules on the extensor surfaces of the forearms (seven out of seven compared with 25 per cent.) and of the combination of splenomegaly and leucopenia (Felty's syndrome) (four out of seven, compared with 10 per cent.). None of the seven patients had clinical evidence of polyarteritis and in no case did the serum produce the L.E.-cell phenomenon or show fixation of complement with a number of "nuclear antigens". No other concurrent disease process could be detected. An increase in the serum γ-globulin content was found in six of the seven (compared with 20 per cent. of the control group) and a marked increase in the serum euglobulin fraction in all (compared with 10 per cent.), the latter being related to the high concentration of the 22-S globulin complex, which is itself a euglobulin. It was demonstrated in one case, in which the serum contained 1,000 mg. 22-S complex per 100 ml., that 40 per cent. of the total γ-globulin content consisted of this material, suggesting that the elevation of the serum γ-globulin content in this patient at least was largely due to the 22-S complex and not to the 7-S component which is usually responsible for hyperglobulinaemia in other disease states. *Harry Coke.*

Two-year Comparative Study of Serial Haemagglutination Tests on Groups of Rheumatoid Arthritis Patients. DE FOREST, G. K., MUCCI, M. B., and BOISVERT, P. L. (1958). *Arthrit. and Rheum.*, **1**, 387. 1 fig., 6 refs.

In a previous paper from the Grace-New Haven Community Hospital and Yale University of Medicine (de Forest *et al.*, *Amer. J. Med.*, 1956, **21**, 897) it was reported that, in ten out of fifteen cases of rheumatoid arthritis undergoing a Grade-I remission, the agglutination reaction with sensitized sheep erythrocytes had become negative. Shortly afterwards the reaction became negative in four more of these cases. This group has now been observed for a further 2-year period and the behaviour of the reaction compared with that in two other selected groups of cases of the same disease in which it followed a different clinical course.

Of the original group of fifteen patients, eleven have remained in complete remission and in ten of these the haemagglutination reaction has remained negative. Four patients suffered clinical relapse and developed a positive haemagglutination reaction; three of these again went into remission and in two the reaction once more became negative. The first of the two contrasting groups was a series of 25 patients with consistently progressive chronic rheumatoid arthritis who had had no remission for 2 years previously and had none during the 2 years of observation. In this group the reaction was consistently positive in moderately high titre (1 : 128 to 1 : 512) except that in two cases a negative result was obtained on one occasion only and without apparent relation to the

clinical status. The second contrasting group consisted of 25 patients with either monarticular arthritis or very mild fluctuating polyarthritis who were diagnosed as having "possible rheumatoid arthritis". Of this group, all but one gave negative haemagglutination reactions. In two cases the condition progressed to typical rheumatoid arthritis, though the negative reaction was maintained.

It is suggested that serial determinations of the haemagglutination reaction have a significance which the single isolated determination does not possess. Broad differences in the pattern of reaction can be distinguished when cases are grouped clinically. In the difficult category of "possible rheumatoid arthritis" the results are not generally diagnostically helpful. Conversion of the reaction from negative to positive occurs fairly promptly in individuals whose disease becomes reactivated, but the conversion from positive to negative during remission may take several months. Minor fluctuations in the clinical course are not reflected in changes of titre. *Harry Coke.*

Heart in Rheumatoid Arthritis. (Cœur et polyarthrite chronique évolutive.) COSTE, F., and DESHAYES, P. (1958). *Rev. Rhum.*, **25**, 697. 21 refs.

The authors review the incidence of clinical cardiac abnormalities in 361 patients with rheumatoid arthritis under treatment at the Clinique Rhumatologique, Paris, and compare it with the incidence among 200 control patients under 60 years of age attending a general medical clinic.

Of the controls, sixteen (8 per cent.) had cardiac signs, among whom were five (2·5 per cent.) without evidence of rheumatic heart disease, syphilis, hypertension, or atherosclerosis. Of the patients with rheumatoid arthritis, 127 were over 60 years old and signs of heart disease in 26 of these were attributed to possible atherosclerosis. Among the remaining 234 who were under 60 years of age, there were 21 with cardiac signs, for which there was no apparent cause in eleven (4·7 per cent.). In these eleven the signs consisted in an apical systolic murmur in four cases and a basal systolic murmur in four, the other three having atrial fibrillation, combined mitral and aortic lesions, and myocardial infarction respectively. [Electrocardiographic and radiological findings are not reported.]

A history of acute rheumatism was obtained in 2·5 per cent. of the controls and 1·2 per cent. of those with rheumatoid arthritis. The authors therefore conclude that these results do not support the existence of a "rheumatoid type" of heart disease. *J. A. Cosh.*

Relationship to Rheumatoid Arthritis of Its So-called Variants. MCEWEN, C., ZIFF, M., CARMEL, P., DITATA, D., and TANNER, M. (1958). *Arthrit. and Rheum.*, **1**, 481. Bibl.

In this paper [the title of which is misleading] the authors report the results of haemagglutination tests in cases of various types of arthritis other than classic rheumatoid arthritis and compare them with those in cases of rheumatoid arthritis and in controls. In addition to the direct sheep erythrocyte agglutination test the inhibition test was performed in all cases, the technique of both tests being that of Ziff and others (*Amer. J. Med.*, 1956, **20**, 500; *Abstr. Wld Med.*, 1956, **20**, 387), using the euglobulin fraction of the serum.

Of 31 patients with Still's disease (that is, with chronic arthritis starting before the age of 12 years), eighteen (58 per cent.) gave a positive reaction to the direct and 29 (95·8 per cent.) to the inhibition test. Of the seven who were adult at the time of testing, four gave a positive direct and six a positive inhibition reaction. One child, who had been ill for less than one year, gave negative reactions to both tests. Out of 120 patients with ankylosing spondylitis, including eighteen with involvement of the peripheral joints, 119 gave negative reactions to both tests, the remaining patient, who had no peripheral involvement, giving a positive reaction to both tests. Among 76 cases of psoriasis with arthritis, equivocally positive reactions to both tests were obtained in one only; this patient and fifty others, who gave negative reactions, had terminal phalangeal involvement. Of 22 patients with arthritis accompanying ulcerative colitis, none gave positive results. Of 41 with Reiter's disease, only one gave positive reactions (to both tests); this man had urethritis, arthritis, keratoderma blennorrhagica, and involvement of the eyes. A positive reaction was obtained to the direct test in 88 per cent. and to the inhibition test in 96·4 per cent. of 140 cases of rheumatoid arthritis, the corresponding figures being 2 and 3·7 per cent. respectively for the 321 control subjects, who included patients with osteo-arthritis, gout, rheumatic fever, and miscellaneous non-rheumatic diseases and normal individuals.

The authors suggest that these results indicate that all the syndromes studied except Still's disease are distinct from rheumatoid arthritis, and this proposition is examined in the light of clinical and pathological data. They point out that although "confusion regarding the relationship of rheumatoid arthritis to its so-called variants appears to be approaching clarification, new confusion has emerged regarding its relationship to . . . the 'collagen diseases' ". Although the latter problem is not discussed in this paper, mention is made of a series of eighteen cases of systemic lupus erythematosus, in five (28 per cent.) of which the result of the inhibition test was positive.

[This is an important and authoritative paper. The results obtained with Ziff's inhibition test are of particular interest since it has not been used to any large extent elsewhere.] *E. G. L. Bywaters.*

Rheumatoid Arthritis and Still's Disease in Children. A Survey of 161 Cases. EDSTROM, G. (1958). *Arthrit. and Rheum.*, **1**, 497. 4 figs, 7 refs.

A series of 161 cases of Still's disease or juvenile rheumatoid arthritis (in children below 15 years of age) treated at the University Hospital, Lund, Sweden, during a period of 20 years is reviewed with special reference to the clinical manifestations and prognosis. Among the 109 girls and 52 boys, only seven presented Still's triad of splenomegaly, hepatomegaly, and lymphadenopathy. A positive throat culture for haemolytic streptococci was

obtained in 48 per cent. and a positive antistreptolysin titre in 51 per cent. of those tested (about two-thirds). In more than 90 per cent. [of an unstated number of cases] a positive Rose-Waaler reaction was obtained. In about one-third the disease began as monarthritis and in ten cases persisted as such throughout. Subcutaneous nodules were rare. Stiffness of the cervical spine occurred in ten cases and spontaneous dislocation of the atlas in two. Cardiac involvement occurred in all the seven patients with Still's triad (two of whom died from heart failure and one from uraemia, amyloid nephrosis being found *post mortem*) and in 33 of the remainder. Iridocyclitis developed in twelve cases and Sjögren's syndrome in one, while one patient had encephalitis with diplopia. Transient exanthemata of various types were commonly seen.

Treatment consisted of rest in bed, bracing, and physiotherapy, together with vitamins, blood transfusions, and salicylates. Chrysotherapy was frequently used up to 1950, since which time adrenocortical hormone therapy has become the standard treatment. Splinting, traction, and physiotherapy were used to prevent or treat contractures and deformities, and rehabilitation devices were employed as indicated.

Five of the patients who had had Still's triad and 85 of those who had had juvenile rheumatoid arthritis were followed up 5 or more years after their discharge from hospital. Of the former, three had died or become bedridden; only the two who had received prolonged hormone treatment were well, although mild symptoms still persisted. Of the latter, 53 patients (62 per cent.) were symptom-free, in sixteen (19 per cent.) the disease was quiescent, though residual articular or ocular defects were present, and eleven (13 per cent.) had died or become invalids; in five cases only was the disease still active. The acute phase had lasted for an average of 2 to 3 years in cases where the patient had subsequently become symptom-free; when it had lasted longer the ultimate prognosis was usually worse.

Of the 24 patients admitted within one year of onset, eighteen (75 per cent.) were symptom-free as against thirteen (54 per cent.) of the 24 patients admitted more than 2 years after the onset. There was little difference in ultimate results between patients treated with salicylates alone and those who had also received gold therapy. Very few of these ninety patients had received steroid treatment, but the findings so far in the remainder of the series do not suggest any improvement in the late results. The author considers that the better prognosis in juvenile rheumatoid arthritis at the present time is due to better general hospital treatment, physiotherapy, and rehabilitation rather than to better medication.

E. G. L. Bywaters.

Tenosynovitis in Patients with Rheumatoid Arthritis. (Tendosynovite chez les patients atteints de polyarthrite chronique évolutive.) ORY, M., and HENRARD, A. (1958). *J. belge Méd. phys. Rhum.*, **13**, 253. 4 figs, bibl.

The first half of this paper consists of a broad outline of the anatomy and physiology of tendons and their synovial sheaths, with particular reference to those of the wrist and hand, followed by brief accounts of each of the inflammatory and traumatic lesions which may be found in these structures and their treatment. The authors then discuss the occurrence of these lesions in rheumatoid arthritis with reference to a personal series of 100 cases (39 in males and 61 in females) selected at random from among patients undergoing thermal treatment at Spa. According to various observers, involvement of the tendons occurs in 42 to 48 per cent. of cases of rheumatoid arthritis.

Tenosynovitis, particularly of the wrist and ankle, is frequently found, more especially in cases of acute onset. It may be accompanied by effusions or be of the dry type with formation of pseudocysts. The authors found tenosynovitis of the hand or wrist in six of their 100 cases, a considerably lower incidence than that reported by others. Altogether ten tendons were affected, nine of them being extensors and only one a flexor. The wrist was the commonest site affected. Nodules were present in the tendons or peritendinous tissues in seven cases, and in this group eight flexor tendons were affected and two extensors. The index was the finger most frequently involved. No case of stenosing tenosynovitis was seen. Spontaneous or traumatic rupture of the tendons has frequently been reported in cases of rheumatoid arthritis. In the authors' series there were three definite cases of spontaneous rupture of one or more tendons at the level of the wrist and two cases of accidental rupture of a single finger tendon. They observed trigger finger in twelve cases, the lesion being at the wrist in one and at the level of the head of the metacarpal bone in the others. Excision of the nodule responsible for this disability is usually out of the question as it would damage the tendon, but the tendon sheath can be slit open or hydrocortisone injected into it. Elongation of the tendons was observed in five cases. Mallet finger occurred in 46 cases and *doigt en boutonnière* in forty, two or more fingers being affected in 34 and 25 cases respectively. The reverse of mallet finger—hyperextension of the proximal interphalangeal joint—was seen in twenty cases. Subluxation of the extensor tendons occurs concomitantly with ulnar deviation of the hand in rheumatoid arthritis and it is impossible to say which is the primary lesion; in recent cases the use of a plaster or plastic cast to correct the deformity is often successful. From a study of the age incidence of the various lesions found in their series the authors conclude that age does not seem to influence the involvement of tendons in rheumatoid arthritis.

William Hughes.

Rheumatoid Tenosynovitis. Diagnosis and Treatment. POTTER, T. A., and KUHNS, J. G. (1958). *J. Bone Jt Surg.*, **40A**, 1230. 3 figs, 12 refs.

Writing from the Robert Breck Brigham Hospital, Boston, the authors discuss the diagnosis and treatment of rheumatoid tenosynovitis. The involvement of tendons and tendon sheaths is relatively common in rheumatoid arthritis and in most cases of the disease these

lesions develop sooner or later. The onset is insidious and often painless, and the course usually slow but progressive. Microscopically, there is proliferation of fibrous tissue in the lining of the sheath and infiltration with small round cells, while the tendon sheath is distended by the increased fluid. Degeneration of the sheath may occur with accumulation of detritus within the sheath; later pannus grows from the sheath into the tendon, and granulomatous nodules appear on the surface of the tendon sheath and tendon. There is ischaemic necrosis with replacement of the tendon by fibrous tissue, and finally adhesions to surrounding tissue or rupture of the tendon as a final result.

In the treatment of small swellings (less than half an inch (1·25 cm.) in diameter) good results may be obtained by suitable plaster splinting and heat; relief was obtained in thirty (46 per cent.) of 65 cases so treated by the authors. If the swelling remains unchanged after several weeks, 25 mg. hydrocortisone may be injected into the swelling; this gave relief in twenty out of 35 such cases. For larger swellings (over 2·5 cm. in diameter) surgical intervention with dissection of diseased tissue may be required; this either arrests the process completely or else delays or prevents degeneration and rupture. If rupture of the tendon occurs, a tendon graft may be substituted for the diseased portion, and various methods are discussed. In the authors' patients, excision of the swelling produced a cure in 66 per cent. of thirty cases and tendon repair led to good function in ten out of 24 cases. The authors consider that any apparent relationship between rheumatoid tenosynovitis and de Quervain's disease or "snapping finger" is only incidental.

D. Preiskel.

Anterior Pituitary Basophils in Rheumatoid Arthritis. BARTHOLOMEW, L. E., SLOCUMB, C. H., and BAHN, R. C. (1958). *Proc. Mayo Clin.*, **33**, 635. 5 refs.

The authors refer to the work of Pearse, who found certain changes in the basophil cells of the anterior pituitary lobe in patients with rheumatoid arthritis, and then report the results of a study of the pituitary glands from eighteen patients with active or inactive rheumatoid arthritis and seven patients without evidence of this disease.

The proportions of various types of basophils present, based on the intensity, morphology, and intracellular distribution of periodic-acid-Schiff-reactive material, were determined. Polar bigranulate cells were observed in almost all sections examined from patients with rheumatoid arthritis, but the proportion of basophils represented by these cells was no greater than in the controls. The proportion of submaximal basophil cells was greater in patients with rheumatoid arthritis who had received cortisone or ACTH (corticotrophin) than in those who had not received steroid therapy. *Oswald Savage.*

Intra-Articular Injections in the Management of Rheumatoid Arthritis. ZUCKNER, J. (1959). *Rheumatism*, 15, 9. 1 fig., 20 refs.

Surgical Relief of Fibrous Ankylosis of the Proximal Interphalangeal Joints in Rheumatoid Arthritis. (Libération chirurgicale de l'ankylose fibreuse des articulations interphalangiennes proximales dans la polyarthrite chronique évolutive.) LOUYOT, P., HAHN, P., and MICHON, J. (1958). *Rev. Rhum.*, **25**, 705. 8 figs, 4 refs.

Hand Lesions in Rheumatoid Arthritis that are Amenable to Surgical Correction. ADAMS, J. P. (1959). *Med. Ann. D.C.*, **28**, 15, 59.

Demineralization of the Finger Bones in Rheumatoid Arthritis. [In English.] LAITINEN, H., VIRKKUNEN, M., and VIRTAMA, P. (1958). *Acta rheum. scand.*, **4**, 266. 2 figs, 9 refs.

Periodic Assessment in Rheumatoid Arthritis. (Bilan périodique dans l'arthrite rhumatoide.) LIÈVRE, J.-A., and DUCANGE, H. (1958). *Rev. Rhum.*, **25**, 714. 10 refs.

Disturbance of Homeostasis between Cortisone and Noradrenalin in Rheumatoid Arthritis. (Die Störung der Cortison-Noradrenalin-Homeostasis bei der primär chronischen Polyarthritis.) MICHOTTE, L. J., and DE VAHIA, M. (1958). *Z. Rheumaforsch.*, **17**, 501. 2 figs, 26 refs.

Clinical Experience of the Agglutination of Collodion Particles sensitized with Gamma Globulin by the Serum of Patients with Rheumatoid Arthritis. (Klinické zkušenosti s aglutinací kolodiových částeček, sensibilisovaných globulinem gama, séry nemocných progresivní polyartiritidou.) LAVICKA, J., and ZAVAZAL, V. (1959). *Čas. Lék. čes.*, **98**, 104. 1 fig., 2 refs.

Gold Treatment in Rheumatological Practice. (La auroterapía en la práctica reumatológica.) HERRERA RAMOS, F., and BARROS, B. (1958). *Arch. interamer. Rheum.*, **1**, 103. 3 figs, 74 refs.

Chrysotherapy in Rheumatoid Arthritis. (La chrysothérapie de la polyarthrite chronique évolutive.) DE PREUX, T. (1959). *Praxis*, **48**, 81. 14 refs.

Treatment of Rheumatoid Arthritis with Chloroquine. (Die Behandlung der chronischen Polyarthritis mit Chloroquin.) DE CHATEL, A. (1959). *Acta med. Acad. Sci. hung.*, **13**, 49. 18 refs.

Contribution to the Study of Rheumatoid Arthritis in Childhood. (Contributo alla conoscenza dell'artrite reumatoide nell'infanzia.) SCANO, V. (1958). *Ann. ital. Pediat.*, **11**, 557. 20 figs, 110 refs.

Still's Disease and Its Nosological Limits. (La malattia di Still e i suoi limiti nosologici.) VERDURA, G., SVILOKOS, N., and SERAFINI, L. (1958). *Minerva pediat. (Torino)*, **10**, 1251. 23 figs, 72 refs.

Primary Chronic Polyarthritis in Children. (La poliartrite cronica primaria infantile.) MONTE, A. D., and DE PASQUALE, F. M. (1958). *Reumatismo*, **10**, 390. 5 figs., bibl.

Cortisone in the Long-Term Treatment of Rheumatoid Arthritis. A Three-Year Study. [In English.] NYFOS, L. (1958). *Acta rheum. scand.*, **4**, 225. 29 refs.

6-Methyl Prednisolone in the Treatment of Rheumatoid Arthritis. MONTGOMERY, D. A. D. (1958). *Ulster med. J.*, **27**, 130. 11 refs.

Comparison between the Antirheumatic Activities of Prednisone and Triamcinolone. (Comparación entre la actividad antirreumática de la prednisona y la triamcinolona.) RUIZ MORENO, A. (1958). *Arch. argent. Reum.*, **21**, 162.

Comparison between the Antirheumatic Activities of Prednisone and Dexametasone. (Comparación entre la actividad antirreumática de la prednisona y la dexametasona.) RUIZ MORENO, A. (1958). *Arch. argent. Reum.*, **21**, 165. 3 refs.

Use of Triamcinolone in Rheumatoid Arthritis and Psoriatic Arthritis. (Triamcinolona: su uso en la artritis reumatoidea y en la asociada con psoriasis.) BOSCH, S. J., MORTEO, O. G., PORRINI, A., CHANES, R., and QUIRNO, N. (1958). *Medicina (B. Aires)*, **18**, 103. 7 refs.

Treatment of Rheumatoid Arthritis with Probecid (Benemid): A Preliminary Report. (Tratamiento de la artritis reumatoidea con Probecid (Benemid): relato previo.) RUIZ MORENO, A., and HALPERIN PINES, A. M. (1958). *Arch. interamer. Rheum.*, **1**, 46. 2 refs.

(Osteo-Arthritis)

Value of Intra-articular Injections in Osteo-Arthritis of the Knee. MILLER, J. H., WHITE, J., and NORTON, T. H. (1958). *J. Bone Jt Surg.*, **40B**, 636. 4 figs, 19 refs.

The investigation reported was undertaken to determine the value of certain intra-articular injections when used alone in the treatment of painful osteo-arthritis, previous reports on the efficacy of the method being difficult to interpret owing to the small number of cases treated or the concurrent use of other methods. Patients with primary osteo-arthritis who had persistent pain and radiological evidence of arthritis and who had not received previous therapy were selected. A single joint, the knee, was chosen so as to avoid inaccuracies arising from comparison of the effects of treatment on different joints, and all clinical assessments were carried out by the same observer, who was ignorant of the type of injection used in any particular case. After the initial assessment, each patient was allotted at random to one of five treatment groups and given a series of five injections at 2-weekly intervals, the solution used being:

(1) lactic acid + procaine (34 patients);
(2) procaine (37);
(3) physiological saline (36);
(4) hydrocortisone (37);
(5) none, a mock injection procedure being carried out.

Each case was reviewed 6 weeks after the end of treatment, when a complete clinical re-examination was carried out, with assessment of joint tenderness, range of movement, presence or absence of a limp, and quadriceps power, the patient's own opinion being elicited only after the examination had been completed. A record of the patient's own opinion of his condition was again made, if possible, at the end of 6 months.

At 6 weeks, 153 of the 181 patients (84·5 per cent.) stated that they had improved, there being no significant difference between the five groups. Objective assessment showed improvement in fifty of the 59 male patients (84·7 per cent.) and in 83 out of 122 females (68 per cent.), there being again no significant differences in either sex between the groups, though the over-all difference between the two sexes was significant ($P<0·05$ for one degree of freedom).

At 6 months the results were much the same, 133 out of 167 patients (79·6 per cent.) stating that they were improved, with no significant differences between the groups.

It is suggested that the satisfaction expressed by the patients depended largely on the psychological atmosphere created, and that if intra-articular injection for osteo-arthritis is decided upon "the least noxious and most economical substance (normal saline) or none at all (mock injection) should be used". *B. M. Ansell.*

Pain in Osteo-Arthritis. Its Inflammatory Nature. (La douleur dans les arthroses. Sa nature inflammatoire.) LAYANI, F., DURUPT, L., and CHAOUAT, Y. (1958). *J. belge Méd. phys. Rhum.*, **13**, 302.

Relationship between Osteo-Arthritis and Rheumatoid Arthritis. (Über den Zusammenhang zwischen Arthrosis und primär chronischer Polyarthritis.) KL[illegible]PER, G. (1958). *Z. Rheumaforsch.*, **17**, 494. 24 refs.

Orthopaedic Aspects of Degenerative Joint Disease. (Die degenerativen Gelenkkrankheiten aus der Sicht des Orthopäden.) HACKENBROCH, M. (1958). *Z. Rheumaforsch.*, **17**, 433. 1 ref.

McMurray's Osteotomy in Osteo-Arthritis of the Hip. TUPMAN, G. S. (1959). *Rheumatism*, **15**, 16. 3 figs, 8 refs.

Course of Osteo-Arthritis of the Hip. (Verläufe von Coxarthrosen.) BELART, W. (1958). *Z. Rheumaforsch.*, **17**, 487. 4 figs, 10 refs.

Conservative and Operative Treatment of Osteo-Arthritis of the Hip. (Zur konservativen und operativen Behandlung der Coxarthrose.) HOHMANN, G. (1959). *Dtsch. med. Wschr.*, **84**, 336, 345, 354. 6 figs.

Inflammatory and Degenerative Arthritis of the Hip. (Coxite et coxarthrose.) MICHOTTE, L. (1958). *J. belge Méd. phys. Rhum.*, **13**, 295. 13 refs.

Inflammatory Episodes in Osteo-Arthritis. (Poussées inflammatoires des arthroses.) COSTE, F., FAULONG, L., and LAURENT, F. (1958). *J. belge Méd. phys. Rhum.*, **13**, 309.

Inflammatory Course of Certain Cases of Osteo-Arthritis and the Sclerotic Type of Arthritis [Arthrosclerosis]. (Evolution inflammatoire de certaines arthroses et évolution scléreuse des arthrites [Arthrosclérose].) FORESTIER, J., CERTONCINY, A., and DESLOUS-PAOLI, P. (1958). *J. belge Méd. phys. Rhum.*, **13**, 323. 3 figs.

Inflammatory Manifestations developing during the Course of Osteo-Arthritis. (A propos des manifestations inflammatoires survenant au cours de l'évolution des arthroses.) RUBENS-DUVAL, A., and VAILLIAUMEY, I. (1958). *J. belge Méd. phys. Rhum.*, **13**, 330.

Inflammatory Signs of Osteo-Arthritis of the Hip. (Signes inflammatoires de la coxarthrose.) LOUYOT, P., and GAUCHER, A. (1958). *J. belge Méd. phys. Rhum.*, **13**, 333.

(Spondylitis)

Aortic Lesion of Ankylosing Spondylitis. ANSELL, B. M., BYWATERS, E. G. L., and DONIACH, I. (1958). *Brit. Heart J.*, **20**, 507.

In a survey conducted at the Post-graduate Medical School of London, two out of 222 patients with ankylosing spondylitis were found to have lone aortic regurgitation. The case histories of these patients are reported. Both suffered from spondylitis with peripheral joint involvement and recurrent iritis, and at intervals of 7 and 12 years after the initial symptoms they developed aortic regurgitation. Electrocardiograms showed prolongation of the PR interval in both cases. One patient died from heart failure and *post mortem* examination revealed thickened aortic valve cusps with rolled margins. The aorta showed patchy intimal thickening and longitudinal wrinkling reminiscent of syphilitic aortitis. Microscopically there was collagenous thickening and vascularization of the aortic valve cusps, and patchy hyaline thickening of the intima of the aorta with perivascular cuffs of lymphocytes around the vasa vasorum and some intimal endarteritis.

In both cases, the diagnosis of syphilitic aortitis was excluded because of negative serological studies including the *Treponema pallida* immobilization test. The authors agree with Bauer and his colleagues that this is a specific aortitis somehow related to the ankylosing spondylitis, and by analogy with the histological changes of syphilitic aortitis the authors suggest that the localization of lesions may be related to the vascular supply.

M. Wilkinson.

Undulant Fever Spondylitis. ZAMMIT, F. (1958). *Brit. J. Radiol.*, **31**, 683. 10 figs, 17 refs.

Undulant fever, which is due to milk-borne infection with *Brucella melitensis*, has long been endemic in Malta; during the period 1947-54 the number of reported cases amounted to 6,301. In this paper from St. Luke's Hospital, Malta, the author reviews 62 cases of the disease seen during this period in which there was definite radiological evidence of involvement of the spine. Brucellar spondylitis mainly affects adults between the ages of 30 and 60 and usually first appears during convalescence or after a period in which only vague symptoms have been present. It is characterized by localized pain in the spine which may be progressive and severe and which may be referred to the limbs in some 60 per cent. of cases. Localized tenderness is surprisingly absent and paraplegia is uncommon.

Radiological changes are likely to develop in an average of 3 months and are more common in males than in females. In the present series the lumbar spine was involved in 37 cases, the dorsal in sixteen, dorsolumbar in four, and the cervical region in five. Two adjacent vertebral bodies are usually affected, but more than one focus of infection may occur:

(1) The vertebral bodies may show (*a*) marginal erosions, which begin in the antero-superior corners, or (*b*) central subchondral areas of destruction; the latter may cause wedging which may be eccentric and produce scoliosis. If the articular surface becomes eroded, the adjacent vertebral body is likely also to be affected. Both lesions provoke a sclerotic reaction with healing and are not accompanied by significant generalized rarefaction. Abscess formation is common in dorsal lesions, but is only rarely encountered in cases of lumbar involvement.

(2) The intervertebral disk space shows early and progressive narrowing, which varies in degree with the extent of the osseous lesions. During healing, however, some restoration of the space may occur.

(3) Proliferative marginal reactions are a characteristic and pronounced diagnostic feature. These are localized round the lesion and first appear as a faint mass of osteoid forming anterior and lateral buttresses, which may later grow together and fuse to form dense amorphous bony structures of irregular shape; these subsequently organize by the formation of lamellar bone and are left as permanent stigmata of the disease. This whole process, unlike that of osteoarthritis from which it must be differentiated, may take place within 3 months, but is noticeably slower in dorsal lesions in which abscesses have formed.

(4) The intervertebral joints, erosions of which have been stressed as a diagnostic feature by other authors, showed no convincing abnormality in this series.

The differential diagnosis is made primarily on the result of the agglutinin test for the presence of undulant fever, but radiologically the features of spinal involvement in this disease lie between those seen in tuberculous infections and those in staphylococcal infections. In the former, the changes occur later, are slower to develop, and there is less sclerosis and proliferative bone reaction.

[Tuberculous abscesses also ultimately show calcification.] Staphylococcal infections cause a more severe illness in which the radiological signs develop earlier, while there is less new bone formation and earlier reactive sclerosis. *R. O. Murray.*

Ankylosing Spondylitis. HART, F. D. (1958). *Brit. med. J.*, **2**. 1082. 4 refs.

An analysis is presented of the replies to a questionary sent to patients treated for ankylosing spondylitis at Westminster Hospital, London, since the war. The questionary was directed towards obtaining information on the general health of the patients, their need for analgesics, and the after-effects of radiotherapy, and of 343 questionaries sent out 200 were returned fully completed, 21 from females and 179 from males.

Of these 200 patients, 160 were working full-time and only nine were completely incapacitated. The author states that these figures are much better than those obtained in patients with rheumatoid arthritis, but because of the number of missing returns (a result of the migratory tendency of these patients) no conclusion could be drawn concerning morbidity. As regards the most useful drugs, aspirin, codeine compound, and phenylbutazone were cited in about equal numbers; 43 patients did not take analgesics regularly. Few of the patients had received steroid therapy. Of 143 who were given radiotherapy to the spine, 114 obtained some benefit. The author states that analysis of the figures for this last group suggests that radiotherapy is followed by some degree of relief for periods up to 7 years in 60 per cent. of cases, temporary improvement in 20 per cent., and no improvement in 20 per cent. Further, there is evidence in these figures which indicates that radiotherapy may have some effect in inducing a remission in ankylosing spondylitis. *B. E. W. Mace.*

Bernard Connor's Description of the Pathology of Ankylosing Spondylitis. BLUMBERG, B. S. (1958). *Arthrit. and Rheum.*, **1**, 553. 3 figs, 10 refs.

Post-traumatic Ankylosing Spondylitis. (A propos de la spondylarthrite ankylosante post-traumatique.) GRABER-DUVERNAY, J., and ARNAUDET, M. (1958). *Rev. Rhum.*, **25**, 803. 4 figs, 38 refs.

Respiratory Function in Ankylosing Spondylitis. (La fonction respiratoire dans la spondylarthrite ankylosante.) BARZIN, J., and FRESON, A. (1958). *J. belge Méd. phys. Rhum.*, **13**, 339. 5 figs, 3 refs.

(Miscellaneous)

Intra-Articular Injections of Hydrocortisone, Prednisolone, and their *Tertiary*-Butylacetate Derivatives in Patients with Rheumatoid Arthritis and Osteo-Arthritis. ZUCKNER, J., MACHEK, O., CACIOLO, C., AHERN, A. M., and RAMSEY, R. (1958). *J. chron. Dis.*, **8**, 637. 14 refs.

The undesirable side-effects so frequently seen after systemic administration of steroids are not observed after intra-articular injection of these drugs. In this paper from St. Louis University School of Medicine, Missouri, a comparative investigation is reported of the efficacy of intra-articular injections of hydrocortisone acetate, prednisolone acetate, hydrocortisone *tertiary*-butylacetate, and prednisolone *tertiary*-butylacetate in the treatment of 34 patients with rheumatoid arthritis and 46 with osteo-arthritis.

In most cases ethyl chloride was sprayed over the injection site; in a few cases an injection of 1 per cent. procaine was given first. The different steroids were administered in rotation, and in both groups of patients the knee-joint was most frequently treated. Injections, each of 25 mg., were given as follows: 208 of hydrocortisone acetate, 185 of hydrocortisone *tertiary*-butylacetate, 203 of prednisolone, and 194 of prednisolone *tertiary*-butylacetate. The period of observation ranged from a few days to 1½ years. All four steroids were equally effective when given in 25-mg. doses, and there was no added benefit when the dose was increased. The response to treatment varied from joint to joint (and even in the same joint) and from patient to patient, the relief obtained lasting an average of 2 to 3 weeks. Out of 53 joints affected with rheumatoid arthritis, good or excellent improvement was achieved in forty, and of seventy osteo-arthritic joints, 59 showed similar improvement.

Discussing the nature of the local action of steroids, the authors point out that hydrocortisone rapidly disappears from a joint, but the fact that it can exhibit oxidation and glycolysis may explain its capacity to suppress the inflammatory reaction. *D. Preiskel.*

Hexylresorcinol (Caprokol) in the Treatment of Arthritis. LIPKIN, E. A. (1958). *Rheumatism*, **14**, 111. 4 refs.

This is a brief report of the treatment in general practice of 165 patients with rheumatoid arthritis or osteo-arthritis by the daily oral administration of "caprokol", "iodolysin", ascorbic acid, and "hypon" [a compound analgesic containing aspirin, phenacetin, codeine, caffeine, and phenolphthalein]. Caprokol is an oily solution of hexylresorcinol, the dose of which ranged from 0·45 to 1·8 g. a day. Iodolysin (thiosinamine ethyl iodine), which is claimed to have a softening effect on cicatrices, was given in a dose of not more than 240 mg. a day. The dose of ascorbic acid was 300 mg. a day. Treatment with caprokol was continued for periods up to 5 years and the dosage was varied according to the needs of the individual patient, but iodolysin was given only for the first 4 months; full details are not given. Improvement was assessed from general mobility, joint circumference, mobility in extension, and grip strength, 104 patients being "much improved", "some improvement" being obtained in fifty others, and little or no improvement in eleven.

[The data contained in this paper are not really sufficient for a critical assessment to be made of the value of these drugs.] *K. C. Robinson.*

Phenylbutazone Therapy in Patients with Rheumatic Disease and Coincidental Essential Hypertension. ZUCKNER, J., AHERN, A. M., MACHEK, O., and CACIOLO, C. (1958). *Amer. J. med. Sci.*, **236**, 460. 4 figs, 7 refs.

In this study, carried out at St. Louis University School of Medicine, Missouri, the authors observed the effect

of intermittent medication with phenylbutazone on the blood pressure and cardiac status of 54 patients, of whom 43 were suffering from osteo-arthritis, six from rheumatoid arthritis, three from chronic bursitis, one from fibrositis, and one from disseminated lupus erythematosus. Their average age was 66, all but two being over 50 years of age, and all but five showed some degree of hypertension before the start of the trial, the systolic pressure in sixteen cases exceeding 200 mm. Hg, while in six the diastolic pressure was over 120 mm. Hg. Phenylbutazone was given intermittently, the initial dose being 200 mg. three times daily for 5 to 7 days except in patients with marked cardiac decompensation, who received a smaller dose. The drug was then withdrawn, a further course at the same or a smaller dosage being given only to those patients who had shown some response on recurrence of symptoms. About half the patients received only one course of treatment, but some of the others were treated intermittently for up to 2 years. [These two groups are not analysed separately.]

In all, ten patients showed an increase in the systolic blood pressure of more than 10 mm. Hg, but in eighteen there was a fall in this pressure of at least 10 mm. Hg; corresponding changes were observed in the diastolic pressures. None of the patients showed any change in cardiac status. Other side-effects were similar to those reported by other workers and included oedema, gastro-intestinal disturbances, leucopenia, and pruritus. Of twelve patients who exhibited some toxic side-effects, the drug had to be withdrawn in four. In general, about two-thirds of the patients in this series obtained some relief of their rheumatic symptoms from the administration of phenylbutazone. *H. F. Reichenfeld.*

Diagnostic Value of Punch Biopsy of the Knee Synovium. MIKKELSEN, W. M., DUFF, I. F., CASTOR, C. W., ZEVELY, H. A., and FRENCH, A. J. (1958). *A.M.A. Arch. intern. Med.*, **102**, 977. 10 figs, 8 refs.

The authors describe, from the University of Michigan, Ann Arbor, the technique of performing punch biopsy of the synovium of the knee-joint with the Polley-Bickel biopsy instrument (illustrated), a procedure which they have found to be "rapid, inexpensive, and sufficiently safe for routine use". This method can be used in a standard treatment room, if necessary on out-patients, under local anaesthesia and with the usual aseptic precautions. In this study biopsy was performed 207 times on 190 patients and was found to be of definite diagnostic aid in 77 cases (40 per cent.), only ten (4 per cent.) of the attempts being unsuccessful.

In cases of rheumatoid arthritis the specimens showed no definite diagnostic features, but in most cases they revealed the presence of hyperplasia of synovial intimal cells, subintimal infiltration with plasma cells and lymphocytes, and generally increased vascularity and oedema. Similar changes were found in the so-called "variants" of rheumatoid arthritis, such as ankylosing spondylitis, Reiter's syndrome, and psoriatic arthropathy. In osteo-arthritis the changes seen were less marked, and such cases were in general easily differentiated. Urate deposits were found in biopsy specimens from one-third of the patients with gout, and lime-salt deposits were found in most cases of neurotrophic joint disease. Specimens of synovium from cases of specific infectious arthritis showed changes that could usually be differentiated from those of rheumatoid arthritis, and were in some conditions (such as tuberculosis) definitely diagnostic. It is suggested that synovial punch biopsy of the knee-joint, together with culture of the synovial fluid, is of particular value in the differential diagnosis of specific infectious arthritis, which is important because of the danger of early irreversible changes and because this is one of the few potentially curable joint diseases.

B. E. W. Mace.

Pseudopolyarthritis of the Shoulder and Hip Girdles. (Pseudopolyarthrite rhizomélique.) FORESTIER, J., and CERTONCINY, A. (1958). *Sem. Hóp. Paris*, **34**, 3220. 7 refs.

Some 6 years ago the authors (*Rev. Rhum.*, 1953, **20**, 854; *Abstr. Wld Med.*, 1954, **16**, 58) described 25 cases of a clinical syndrome for which they suggested the name *pseudopolyarthrite rhizomélique*. Since then they have observed, at the Rheumatic Clinic, Aix-les-Bains, 23 further similar cases, and now present a more complete and detailed description of this syndrome.

It is essentially a disorder of the second half of life, affecting both men and women; of the authors' 48 patients, eighteen were men and thirty women, ranging in age from 48 to 81 years. It is often accompanied by fever, the temperature rising to 100° or 101° F. (37·8° to 38·3° C.), and is characterized by severe pain and restricted movement in both shoulders and, to a lesser degree, in the hip and lumbar regions. No other joints are affected, except in some cases by fleeting pains. There are no significant radiological changes in the shoulder, hip, or sacro-iliac joints. The erythrocyte sedimentation rate is always increased, usually considerably, in some cases to as much as 100 mm. in one hour. There may be a moderate anaemia and rarely a leucocytosis.

In some of the authors' patients the condition had been present for as long as 18 months before they were first seen, but during this time there had been no amelioration. Although the disorder is apparently not progressive, spontaneous recovery may thus nevertheless be exceedingly slow. All the patients in the earlier series were treated by injection of gold or copper and all recovered without sequelae within a few months to a year. In the present series eight of the patients were treated with adrenocortical steroids. Improvement was prompt, but each attempt to stop administration of the hormone at intervals of a few weeks was followed by relapse. In three cases the patients have received a maintenance dose of prednisone of 3 to 5 mg. daily for 6 to 9 months; in one of these cases slight symptoms recurred on stopping administration after 6 months.

The syndrome can be distinguished from a rhizomelic form of rheumatoid arthritis by the fact that no synovial swelling or effusion can be detected in the shoulder-joints. All the patients have recovered, with no residual joint signs, and have remained free from recurrence.

The condition is clearly not the common scapulo-humeral periarthritis, nor ankylosing spondylitis, nor a manifestation of one of the known collagen diseases. The authors are convinced that it is a periarticular affection.

[This is an important and little known syndrome, and is undoubtedly a distinct clinical entity. It has not, however, been very happily named, and possibly "rhizomelic periarthritis" would be better, or, until its nature becomes clear, simply "the syndrome of Forestier and Certonciny".] *Kenneth Stone.*

Controlled Trial of Various Forms of Physiotherapy in Arthritis. HAMILTON, D. E., BYWATERS, E. G. L., and PLEASE, N. W. (1959). *Brit. med. J.*, **1**, 542.

In the authors' experience a critical, quantitative assessment of the results of physiotherapeutic measures is carried out at comparatively few centres. In general, degenerative joint disease of the knees and rheumatoid arthritis of the knee or hand are treated by a basic regimen consisting of exercises, analgesics, splintage, and encouragement. In an attempt to determine whether, in the treatment of such conditions, the addition of short-wave diathermy, infra-red irradiation, faradic stimulation, or paraffin-wax baths makes any difference to the results obtained, the authors have carried out at Hammersmith Hospital (Post-graduate Medical School of London) a controlled trial designed to answer this question and also to determine which of these additional procedures produces the greatest functional improvement, if any, during one month's treatment.

Each of 62 patients (out of 131 initially selected) completing the trial was given one of the following four treatments in random order:

(A) dummy short-wave diathermy (current not turned on) as a control;
(B) short-wave diathermy;
(C) infra-red irradiation;
(D) either faradism (for knees) or wax treatment (for hands).

Each treatment was given for one month and assessment was made at its beginning and end. Knees were assessed in respect of range of movement, quadriceps power, "stair time" (that is, the time taken to walk up and down four standard steps), and "walking time" (time taken to walk 20 yards). Hands were assessed with regard to power of grip, range of wrist movement, and "knot time" (time taken to tie three knots).

In general there was an over-all improvement from the beginning to the end of each month; but no evidence could be found of any significant difference between the results of the three treatments and those observed after dummy exposure to short-wave diathermy. Further, the authors conclude that improvement could have been due solely to the basic regimen, as outlined above. They are aware, however, of the fundamental difficulties of such a trial, and point out that in spite of their conclusion it is still possible that the therapeutic measures studied may be useful adjuncts to the basic regimen.

Kenneth Stone.

Results obtained with Intra-Articular Trimethyl Prednisolone Acetate ("Ultracortenol"). (Resultados obtido com o uso do Trimetilacetato de Prednisolona [Ultracortenol] intra-articular.) DE FREITAS, G. G. (1958). *Arch. interamer. Rheum.*, **1**, 514. 2 refs.

Comparative Studies of the Antirheumatic Action of Prednisone, Triamcinolone, and Dexamethasone. (Ricerche comparative sull'azione antireumatica del prednisone del triamcinolone e del desametasone.) DANEO, V. (1958). *Reumatismo*, **10**, 387. 6 refs.

A Study of Four Cases of "Psoriatic Arthropathy" with Special Reference to the Histological Findings. (Studio di quattro casi di "artropatia psoriasica" con particolare riferimento al quadro istologico.) GARELLI, R., and MARRAZZI, G. (1958). *Reumatismo*, **10**, 351. 6 figs, 27 refs.

Schoenlein-Henoch Purpura. A Clinical Study in Adults. (Le purpura de Schoenlein-Henoch. Etude clinique chez l'adulte.) HUGUES, J., LECOMTE, J., and DUPONT, M. (1958). *Acta clin. belg.*, **13**, 460. 26 refs.

Articular and "Rheumatic" Manifestations of Leukaemia. (Sulle manifestazioni articolari e "reumatiche" delle leucemici.) GARELLI, R. (1958). *Reumatismo*, **10**, 341. 33 refs.

Disk Syndrome

Another Look at the Problem of Lumbo-Sacral Pain and Sciatica. KING, T. (1959). *Med. J. Aust.*, **1**, 8. 11 refs.

Gout

Diagnosis of Gout. Significance of an Elevated Serum Uric Acid Value. GOLDTHWAIT, J. C., BUTLER, C. F., and STILLMAN, J. S. (1958). *New Engl. J. Med.*, **259**, 1095. 28 refs.

Between 1949 and 1956 a total of 225 patients at the Robert Breck Brigham Hospital, Boston, were found to have serum uric acid levels above 6 mg. per 100 ml. as determined by the Archibald modification of the Kern-Stransky method. Only 113 of these patients had gout; in the remaining 112, rheumatoid arthritis and a wide range of miscellaneous conditions were diagnosed (the majority of patients attending this hospital had some type of bone or joint disease). Polycythaemia, leukaemia, or myeloma was not encountered and there were two cases of renal disease. Since only six of the 112 patients gave a positive family history of gout, this was not an important factor in explaining the high serum uric acid levels.

Although the authors do not discuss the serum uric acid levels in the general population, they do refer to the many workers who have found that values greater than 6 mg. per 100 ml., are not uncommon in the general population. They consider that in their series they observed the random occurrence of hyperuricaemia.

K. C. Robinson.

Gout in the Female. (La gota en la mujer.) RUIZ MORENO, A. (1958). *Arch. argent. Reum.*, **21**, 149. 27 refs.

Gout and Urinary Lithiasis. (Gota y litiasis urica.) RUIZ MORENO, A. (1958). *Arch. argent. Reum.*, **21**, 156. 15 refs.

Incorporation of Glycine-1-C^{14}, Glycine-2-C^{14}, and Glycine-N^{15} into Uric Acid in Normal and Gouty Subjects. GUTMAN, A. B., YÜ, T. F., BLACK, H., YALOW, R. S., and BERSON, S. A. (1958). *Amer. J. Med.*, **25**, 719. 12 figs, 23 refs.

New Comments of the Metabolism of Gout. (Nové poznatky v metavolismu dny.) BLAHOŠ, J., and LAVICKA, J. (1959). *Čas. Lék. čes.*, **98**, 266. 97 refs.

Pararheumatic (Collagen) Diseases

Renal Function in Scleroderma. URAI, L., NAGY, Z., SZINAY, G., and WILTNER, W. (1958). *Brit. med. J.*, **2**, 1264. 1 fig., 34 refs.

An investigation of renal function in 25 patients with scleroderma of varying severity is reported from the University of Budapest. The effective renal plasma flow, as measured by PAH clearance, was reduced in over 80 per cent. of the cases, whereas the glomerular filtration rate, which was studied by the endogenous creatinine clearance method, was normal in 23 of the 25 cases, and moderately reduced in the other two. The filtration fraction was computed from these values and found to be much increased in nineteen out of the 25 cases. It is concluded that this indicates that the anatomical renal changes are accompanied by spasm of the efferent vessels, possibly as a compensatory mechanism designed to maintain good glomerular function in the presence of renal vascular lesions. It is considered that the finding of a reduced renal plasma flow in patients with this disorder gives an earlier indication of sclerodermal renal involvement than do other clinical tests.

G. W. Csonka.

Reaction of Lupus Erythematosus Serum with Nuclei of Circulating and Non-circulating Cells. ALEXANDER, W. R. M., and DUTHIE, J. J. R. (1958). *Brit. med. J.*, **2**, 1565. 8 refs.

In the study here described from the Northern General Hospital, Edinburgh, the authors used the fluorescent antibody technique to confirm that the serum of patients with disseminated lupus erythematosus (D.L.E.) contains a globulin which combines with tissue nuclei. Untreated tissue from patients with D.L.E. showed no evidence of globulin being adsorbed *in vivo*.

After exposure to eight D.L.E. sera, nuclear fluorescence (indicating globulin uptake) was manifested by all of eight preparations of normal Group-O leucoctyes, but only by six out of eight preparations of autologous leucocytes; also by six out of eight preparations of healthy skin, but only three out of eight of autologous skin. The authors suggest that tissue from patients with D.L.E. has less than normal affinity for lupus globulin.

[In a study on so few patients and with such a tricky technique, this conclusion seems unconvincing.]

M. Wilkinson.

Polyarteritis Nodosa with Ophthalmic and Neurological Complications. SHEENAN, B., HARRIMAN, D. G. F., and BRADSHAW, J. P. P. (1958). *A.M.A. Arch. Ophthal.*, **60**, Pt. 1, 537. 6 figs, 26 refs.

The authors describe in great detail a case of a woman aged 35, who for 4 years had had intermittent attacks of diarrhoea, vomiting, and loss of weight. In the last year before death she also developed polyneuritis and epilepsy, and she died in a coma.

Two years before her death, the right eye became affected. The visual acuity fell progressively to counting fingers. There was a mild chronic anterior uveitis and the fundus picture consisted of multiple retinal haemorrhages, massive white exudates, retinal oedema, and papilloedema. The right eye was subsequently enucleated and examined histologically.

At the *post mortem* examination, marked fibrotic changes were noted in the ileum and meninges, and areas of infarction of the brain, but examination of the blood vessels revealed nothing specific. Histological examination of the eye revealed, apart from uveitis, typical appearances of the various stages of polyarteritis nodosa in the retinal vessels.

Ophthalmic involvement in cases of polyarteritis nodosa is said to be 10-20 per cent. This case is noteworthy for the unusual fundus picture and because the eye lesions were the means of establishing the diagnosis.

Noel S. Moores.

Clinical Diagnosis of Systemic Lupus Erythematosus. ARMAS-CRUZ, R., HARNECKER, J., DUCACH, G., JALIL, J., and GONZALEZ, F. (1958). *Amer. J. Med.*, **25**, 409. 34 refs.

The authors present a review of the findings in 108 cases of systemic lupus erythematosus (L.E.) admitted to the Hospital San Juan de Dios, Santiago, Chile. Arthralgia or arthritis of the upper extremities was found in 91 per cent. of cases, and classically responded to steroid therapy (cortisone); joint deformity was rare. Among the other features were protein and pleomorphic rashes, including a psoriatic form, but particular emphasis is laid on the presence of alopecia, and the characteristic, thin, lustreless "lupus" hair. Chemosis and nail-bed telangiectasis were considered to be useful diagnostic features. Gastro-intestinal symptoms were common but non-specific; hepatitis was frequently present, but was indistinguishable from other forms of hepatitis. A dominant feature was involvement of the serous cavities, the pleural cavity being involved unilaterally or bilaterally in 56 per cent. of the cases; L.E. cells, however, were not found in the pleural exudates. Cardiac involvement, as manifested by tachycardia, triple rhythm, endocardial and exocardial murmurs, was noted in 88 per cent. of the patients. Libman-Sacks verrucous endocarditis, which is pathognomonic of the disease, produces no

clinical signs, and is purely a *post mortem* finding. Splenomegaly occurred in 19 per cent. of cases and was occasionally associated with either thrombocytopenia or haemolytic anaemia. Various clinical syndromes, including cranial nerve palsies and myelitis, were noted as the result of involvement of the central nervous system. In 15 per cent. of these cases systemic lupus erythematosus had been preceded by Raynaud's phenomenon.

Laboratory investigations, which are described in some detail, confirmed the almost specific nature of the L.E.-cell test in experienced hands; the reaction was positive in 90·4 per cent. of cases in this series, although it was negative in a few cases in which the presence of L.E. was confirmed at necropsy. A raised erythrocyte sedimentation rate and increased γ-globulin levels were found with the usual frequency. Renal function tests revealed renal involvements in 76 per cent. of the cases, although serious azotaemia was relatively uncommon.

[Although this communication adds little that is new to our knowledge of this disease, it is nevertheless a useful retrospective analysis.] *J. N. Harris-Jones.*

Systemic Lupus Erythematosus. Results of Treatment with Triamcinolone. DUBOIS, E. L. (1958). *Calif. Med.*, **89**, 195. 1 fig., 11 refs.

A series of 29 patients with systemic lupus erythematosus were treated with triamcinolone at the Los Angeles County General Hospital for an average of 4 months. The usual maintenance dose necessary to control mild exacerbations was 26 mg. a day. No prophylactic measures against the development of peptic ulcer were taken except when specifically indicated. Of sixteen patients who underwent periodic *x*-ray examination, only one, who was receiving 96 mg. daily, was shown to develop a peptic ulcer. Serial histamine test meals in nine cases revealed no abnormality. The clinical manifestations of the disease were suppressed in the same way by triamcinolone as by the older steroids, though long-standing renal involvement was not affected. During treatment with triamcinolone there was progressive loss of weight, and cutaneous side-effects such as Cushingoid appearance, striae, and hirsutism were more marked than with other steroids. In six cases profound muscle weakness, particularly of the quadriceps group, occurred.

The author concludes that since triamcinolone is more liable to produce cutaneous side-effects than the older hormones, it cannot be regarded as the drug of choice for beginning therapy in the average case of systemic lupus erythematosus. *Oswald Savage.*

Electromyographic and Electroencephalographic Aspects of the Collagen Diseases. (Aspetti elettromiografici ed elettroencefalografici delle malattie del collageno.) ASCIONE, A., COLTORTI, M., SERRA, C., and LAMBIASE, M. (1958). *G. Clin. med.*, **39**, 1819. 19 figs, 40 refs.

Recent Advances in Connective-Tissue Research. (Neuere Ergebnisse der Bindegewebsforschung.) HARTMANN, F. (1958). *Z. Rheumaforsch.*, **17**, 445. 8 figs, 83 refs.

Diffuse Collagen Diseases and their Ocular Manifestations. BIDYADHAR, N. K. (1959). *Antiseptic*, **56**, 29. 22 refs.

Serum Transaminase Activity in Dermatomyositis. (La actividad transaminasica del suero en la dermatomiositis.) PUCHOL, J. R., and CARBALLIDO, A. (1958). *Act. dermo-sifiliogr. (Madr.)*, **49**, 528. 12 refs.

Lipoid Dermato-Arthritis. (Reticulohistocytosis.) LYELL, A., and CARR, A. J. (1959). *Brit. J. Derm.*, **71**, 12. 28 refs.

Dermatomyositis and Systemic Lupus Erythematosus in Childhood. BRUNSTING, L. A. (1959). *J. Okla. St. med. Ass.*, **52**, 9. 11 refs.

Pleuropulmonary Manifestation of Systemic Lupus Erythematosus. (Le manifestazioni pleuropolmonari del lupus eritematoso sistemico.) D'AMBROSIO, R., DI PAOLO, A., and PETRECCA, L. (1958). *Lotta c. Tuberc.*, **28**, 923. 14 figs, 21 refs.

Pleuropulmonary *X*-Ray Findings in Systemic Lupus Erythematosus and Rheumatoid Arthritis. [In English.] AHO, A., JULKUNEN, H., and KAIPAINEN, W. J. (1959). *Ann. Med. intern. Fenn.*, **48**, Suppl. 28, p. 16. 4 figs, 18 refs.

Renal Forms of Libman-Sachs Disease or Disseminated Lupus Erythematosus. (Les formes rénales de la maladie de Libman-Sachs ou lupus érythémateux disséminé.) DÉROT, M., GOMELSKY, J., and ROUDIER, M. (1958). *Sem. Hôp. Paris*, **34**, 3059. 5 figs, 14 refs.

Widal's Reaction in Disseminated Lupus Erythematosus. (La réaction de Widal dans le lupus érythémateux disséminé.) PURRIEL, P., PERONI, R., PUIG, P. G., and MURAS, O. (1959). *Sem. Hôp. Paris*, **35**, 103. 4 refs.

Oedematous Forms of Disseminated Lupus Erythematosus. (Las formas edematosas del lupus eritematoso diseminado.) GARCÍA DEL RIO, C. (1959). *Clin. y Lab.*, **67**, 111. 2 figs.

Treatment of Scleroderma. WINKELMANN, R. K., and BRUNSTING, L. A. (1959). *Minn. Med.*, **42**, 13. 15 refs.

Electrocardiographic Changes in Progressive Systemic Sclerosis (Scleroderma). [In English.] GABOR, G., and URAI, L. (1959). *Acta med. Acad. Sci. hung.*, **13**, 93. 3 figs, 31 refs.

Sclerodermal Disease of the Oesophagus, Sclerodermal Acquired Short Oesophagus or, Sclerodermal Brachy-oesophagus. (Les oesophagopathies sclérodermiques, l'oesophage court acquis sclérodermique, ou brachy-oesophage sclérodermique.) MAZZEI, E., and D'ALOTTO, V. (1958). *Presse méd.*, **66**, 2056. 6 figs, 9 refs.

Radiological Changes in the Oesophagus in Scleroderma. (Les modifications radiologiques de l'oesophage en sclérodermie.) SCHMITZER, G., SCHMITZER, G., and ZISSU, I. (1958). *Presse méd.*, **66**, 2067. 11 figs, 16 refs.

Digestive Manifestations of Scleroderma. (Les localisations digestives de la sclérodermie.) DISSARD, P., CLEMENTI, R., and VACHON, A. (1958). *Rev. lyon. Méd.*, **7**, 1185. 5 figs, 111 refs.

Semeiological and Functional Investigation of the Heart in Scleroderma. (L'esplorazione semeiologica e funzionale del cuore nella sclerodermia.) PENDE, G., GATTO, E., and SOLARI, S. (1958). *Arch. E. Maragliano Pat. Clin.*, **14**, 1215. 6 figs, 55 refs.

Scleroneuropathy. Involvement of the Peripheral Nerves in General Progressive Scleroderma. (Über die Skleroneuropathie, die Mitbeteiligung der peripheren Nerven bei der algemeinen progressiven Sklerodermie.) ZÜLCH, K. J. (1959). *Dtsch. Z. Nervenheilk.*, **179**, 1. 11 figs, 24 refs.

Periarteritis Nodosa. Report of Three Cases successfully treated with Cortisone and ACTH. [In English.] YONIS, I. Z. (1959). *Ann. paediat. (Basel)*, **192**, 65. 11 figs, 49 refs.

Gastro-enterological Aspects of Periarteritis Nodosa. NIGHTINGALE, E. J. (1959). *Amer. J. Gastroent.*, **31**, 152. 119 refs.

Non-Articular Rheumatism

Muscular Rheumatism. (Reumatismo muscular.) USOHIAGA, J. LUIS DE (1959). *Rev. argent. Reum.*, **23**, 371.

Tendinosis and Tenoperiostosis. Tendinosis Syndrome. (Über Tendinosen und Tendoperiostosen. Die Tendinosenkrankheit.) JUNG, A. (1959). *Praxis*, **48**, 73. 2 figs, 23 refs.

General Pathology

Observations concerning the Reactivity of Normal and Rheumatoid Gamma Globulins in Rheumatoid Serological Reactions. MANNIK, M., BRINE, K. L., and CLARK, W. S. (1958). *Arthrit. and Rheum.*, **1**, 410. 15 refs.

This investigation comes from the arthritis unit of the School of Medicine, Western Reserve University, Ohio. It compares the behaviour of Fraction II gamma globulin from the sera of rheumatoid arthritis patients with that from normal subjects in rheumatoid serological reactions. In addition, the reaction of unheated and heated gamma globulin was investigated. The tests included the heterophile absorbed sheep cell test, the coated tanned sheep cell test, the latex particle test, the euglobulin inhibition test, and the Fraction II precipitation test. It was shown that the Fraction II of gamma globulin sera of rheumatoid and non-rheumatoid subjects behaved in a similar fashion both as a sensitizing agent and as an inhibitor in the five tests for rheumatoid arthritis. The rheumatoid agglutinating factor and the gamma globulin factor were found to coexist in sera of patients with rheumatoid arthritis. Heating at 63° C. for 10 minutes increased the affinity of gamma globulin for the rheumatoid agglutinating factor. *G. W. Csonka.*

Chromatographic and Electrophoretic Studies of the L.E. Factor. FALLET, G. H., LOSPALLUTO, J., and ZIFF, M. (1958). *Arthrit. and Rheum.*, **1**, 419.

Working at the New York University College of Medicine, the authors have attempted to characterize and partially purify the L.E. factor. Serum or euglobulin were fractionated on a cation exchange column (carboxymethyl cellulose) and the fractions after elution with solutions of increasing pH and molarity were dialysed against a phosphate buffer to precipitate euglobulin. The euglobulin fractions were dissolved in normal human serum for L.E. cell testing or in buffer solution for electrophoresis.

Chromatographic fractions from normal serum showed no L.E. factor activity even when concentrated up to thirty times.

Studies on serum and on concentrated euglobulin solutions from patients with systemic lupus erythematosus demonstrated the L.E. factor in fractions eluted at pH 6·5 and to a greater extent at pH 7·0. Both of these fractions consisted of gamma globulin. Zone electrophoresis of these two fractions on polyvinyl chloride at pH 6·8 and 8·6 revealed that the L.E. factor activity was confined to a gamma globulin component with retrograde mobility. The redissolved euglobulin prepared from eluate recovered at pH 7 and containing L.E. factor was ultracentrifuged and found to contain material with a sedimentation coefficient of approximately 7. This is the sedimentation coefficient of most gamma globulins excluding the rheumatoid factor.

Investigation of a serum containing both rheumatoid and L.E. factors showed that the rheumatoid factor was present only in the fraction eluted at pH 6·5, whereas the L.E. factor occurred in fractions eluted at pH 6·5 and 7.

The authors consider that chromatographic, electrophoretic, or salt fractionation procedures alone are unlikely to lead to the isolation of highly purified L.E. factor. *M. Wilkinson.*

Rheumatic Process in the Left Auricular Appendage. LANNIGAN, R. (1959). *J. Path. Bact.*, **77**, 49. 20 figs, 31 refs.

The rheumatic process in the left auricular appendage was studied in the Department of Pathology, University of Birmingham, in 175 biopsy specimens obtained at mitral valvotomy. Most of the patients were aged 30 to 39 years, and all had been deemed to be clinically free from active rheumatic disease at the time of operation. In fifteen of these cases necropsy was performed subsequently. In addition, 61 hearts showing macroscopic evidence of rheumatic disease were examined. For control purposes both the left and the right auricular appendage obtained at ninety consecutive necropsies

and 25 whole hearts were studied. There were no lesions like Aschoff nodes and no cellular foci in the subendocardium or endocardium in any of these control cases. Interstitial haematoxyphil substance (resembling the "mucoid oedema" described by Talalajew) was seen in four cases, and in a few the epicardium showed focal lymphocyte collections.

Of the 175 biopsy specimens, 103 contained Aschoff bodies, usually in the subendocardium. The less specific changes of diffuse cellular exudate in the endocardium and subendocardium were present in 63 of these cases, associated with interstitial haematoxyphil substance. In nine cases non-specific changes only were present. The author suggests that such non-specific changes may be considered to indicate a rheumatic process. Auricular thrombus, a condition which is often associated with subendocardial inflammation, was observed in fifty of the specimens.

Of the fifteen cases which came to necropsy after valvotomy, six in which Aschoff nodes had been seen in the auricle also showed these in the ventricular myocardium. In one case there were Aschoff nodes in the ventricle when none had been found in the auricle, and in seven there were no Aschoff nodes in either situation. Of the 61 hearts showing macroscopic evidence of rheumatic disease, lesions were present both in the left auricular appendage and elsewhere in the heart in ten and in the ventricle only in two. *G. Loewi.*

Latex-Fixation Test in Rheumatoid Arthritis. BURBY, G., and BEHR, G. (1958). *Lancet*, **2**, 1157. 3 refs.

The latex fixation test of Singer and Plotz and a modification using bovine γ-globulin are described. Both tests were found to be as sensitive and specific as the Waaler-Rose test.—[*Authors' summary.*]

Studies on the Latex-Fixation Test. [In English.] HEDBERG, H. (1958). *Acta rheum. scand.*, **4**, 257. 10 refs.

In the study here reported from the University Hospital, Lund, Sweden, the titre of the euglobulin fraction of serum as determined by the latex-fixation test of Singer and Plotz was compared with that of whole serum in 38 patients with rheumatoid arthritis and 42 control subjects. In patients with early rheumatoid arthritis and in cases which had been treated with corticosteroid derivatives the latex-fixation titre was more often found to be positive in the euglobulin fraction than in the whole serum. Prozone phenomena were often seen in dilutions of whole serum, but rarely in those of the euglobulin fraction. An adaptation of the inhibition test of Ziff and others (*Amer. J. Med.*, 1956, **20**, 500; *Abstr. Wld Med.*, 1956, **20**, 387) for the latex gamma-globulin system was not successful and only emphasized the differences between the latex test and the sensitized sheep-cell system. *G. W. Csonka.*

Some Aspects of the Intracutaneous Congo Red Test for Rheumatoid Arthritis. [In English.] KIRPILÄ, J. (1958). *Acta rheum. scand.*, **4**, 276. 2 figs, 9 refs.

At the Rheumatism Foundation Hospital, Heinola, Finland, the Congo red test was performed by giving an intracutaneous injection of 0·1 ml. of a 1 per cent. saline solution of the dye to 115 patients with rheumatoid arthritis and thirty control subjects at symmetrical sites on the volar and dorsal aspects of the arms and on the back and thighs. The colour reaction was more intense and persistent in the rheumatoid group than in the controls. A positive correlation between severity of the rheumatoid arthritis and intensity of the colour reaction was established. Of the several areas tested the skin of the thigh gave particularly clear results and is recommended as the standard site. *G. W. Csonka.*

Inhibition of Leucocyte Agglutination by Serum from Patients with Systemic Lupus Erythematosus: a Manifestation of the L.E Cell Phenomenon. LEE, S. L. (1958). *Blood*, **13**, 778. 2 figs, 18 refs.

The author observed that the tendency of leucocytes suspended in normal serum to undergo spontaneous agglutination owing to cell death, lysis, and formation of nucleoprotein "clot" was accelerated in the presence of quinacrine hydrochloride (final concentration 0·2 to 0·4 mg. per ml.), and was invariably complete after 3 hours' incubation at 37° C., but that agglutination failed to occur in the presence of serum containing the lupus erythematosus (L.E.) factor. In this report from the Mount Sinai Hospital, New York, he discusses the various factors influencing this leucocyte agglutination inhibition (L.A.I.) and its value in diagnosis. That the lack of agglutination in the presence of L.E. serum was due to the presence of an inhibitory factor rather than to the absence of an agglutinating factor was suggested by the fact that the ability to inhibit agglutination could be conferred on normal serum by the addition of a small volume (about 6 per cent.) of L.E. serum. Leucocyte agglutination did occur in the absence of quinacrine, but was delayed. Normal serum seemed to be essential for leucocyte agglutination, which was absent or unsatisfactory in solutions of sodium chloride, albumin, and gamma globulin. Examination by the phase-contrast microscope of leucocyte suspensions in normal serum showed that before agglutination began many cells "exploded" and the nuclei of these lysed cells stretched into fibrous strands to enmesh the intact cells.

When leucocytes were incubated with L.E. serum in the presence of quinacrine, smears from the sediment showed swelling and homogenization of all nuclei, with the production of L.E. bodies, but phagocytosis to produce L.E. cells did not occur. Control preparations using L.E. serum without quinacrine showed that most cell nuclei retained their normal structure, but rosette formation and some L.E. cells were easily demonstrable. Leucocyte agglutination was inhibited in the presence of deoxyribonuclease, but the nuclear changes differed from those seen in the presence of L.E. serum; further, although the addition of sodium oxalate reversed the inhibition caused by deoxyribonuclease (by removing magnesium ions) it did not affect the inhibition due to L.E. serum. Inhibition of leucocyte agglutination could not be demonstrated when platelet-poor L.E. plasma was substituted for L.E. serum.

Parallel L.A.I. and L.E.-cell tests were performed on

1,183 specimens of blood. The L.E.-cell reaction was positive in 68 per cent. and the L.A.I. reaction in 59 per cent. of 164 specimens from 34 patients with clinical systemic lupus erythematosus, and in only one instance was the L.A.I. reaction positive when the L.E.-cell reaction was negative. In similar studies carried out on 1,019 specimens of blood from cases of other diseases the L.A.I. reaction was positive in twelve cases, but the L.E.-cell reaction in none. The author suggests that both L.E. serum and deoxyribonuclease interfere with leucocyte agglutination by altering deoxyribonucleoprotein, though in different ways. Although the L.A.I. test is simple to perform, it is less specific than the L.E.-cell test, and it is inadequate as a primary test for systemic lupus erythematosus. *M. Wilkinson.*

Complement-Fixation Reaction with DNA and Leucocyte Material in Systemic Lupus Erythematosus. Correlation with the L.E. Cell Phenomenon and the Clinical Status. PEARSON, C. M., CRADDOCK, C. G., and SIMMONS, N.S. (1958). *J. Lab. clin. Med.*, **52**, 580. 1 fig., 8 refs.

Recent work has shown that complement-fixing reactions occur between a constituent of the serum γ-globulin fraction of some patients with systemic lupus erythematosus (possibly identical with the L.E.-cell factor) and cell nuclei, nucleoprotein, or deoxyribonucleic acid (DNA). This paper from the University of California School of Medicine, Los Angeles, describes the results of such complement-fixation tests on sera from patients with systemic lupus erythematosus and other diseases and correlates them with the occurrence of the L.E.-cell phenomenon. Tests were performed in parallel with DNA prepared from normal human spleen and with nuclear material from lysed human leucocytes as the "antigens".

Of twenty sera from patients with systemic lupus erythematosus, seven gave a positive complement-fixation reaction with DNA, while five out of sixteen gave a positive reaction with leucocyte material. In no case were the results discordant. Positive complement-fixation reactions occurred only with sera from patients with severe or moderately severe disease, usually giving a strongly positive L.E.-cell reaction. The result was negative in all cases in which the disease was only mildly active and in three in which it was more severe. In one case a positive complement-fixation reaction with leucocyte material was obtained before the reaction with D.N.A. and the L.E.-cell reaction became positive. The authors suggest that this finding supports the hypothesis that a separate serum factor is responsible for each of the three reactions.

Complement-fixation tests were carried out with the same "antigens" on sera from 38 patients with various rheumatic and collagen diseases and from fifteen with miscellaneous non-rheumatic diseases. In all cases the results were negative. *M. Wilkinson.*

Clinical Application of a Test for Lupus Globulin-Nucleohistone Interaction using Fluorescent Antibody. FRIOU, G. J. (1958). *Yale J. Biol. Med.*, **31**, 40. 1 fig., 12 refs.

The author has previously demonstrated by the fluorescent antibody technique that a globulin factor in serum from patients with disseminated lupus erythematosus (D.L.E.) reacts with the nucleoprotein component of cell nuclei (*J. Immunol.*, 1958, **80**, 324; *Abstr. Wld Med.*, 1959, **25**, 2). The activity of such sera can be titrated against a nucleohistone extract of calf thymus, and in this further paper from the Veterans Administration Hospital, West Haven, Connecticut, and Yale University School of Medicine a technique developed for this purpose is described and the results obtained with sera from 369 patients with various diseases are reported.

The test gave a positive result with all of 35 sera from patients with D.L.E. Positive results were also obtained in four of 42 cases of rheumatoid arthritis, one of three cases of scleroderma, one of two cases of dermatomyositis, four of seventeen cases of chronic biological false positive reaction to serological tests for syphilis, and one of sixteen cases of drug-sensitivity rashes. Sera from five patients with discoid L.E. gave negative results. Of the other sera tested, positive results were obtained only with two from patients considered to have latent syphilis (though since the treponemal immobilization test had not been performed the possibility of biological false positive reactions could not be excluded) and one from a patient with advanced bronchogenic carcinoma. The positive reactions with sera from patients considered not to have D.L.E. were of relatively low titre with the exception of two cases of rheumatoid arthritis, in both of which there were features suggestive of D.L.E. In cases of D.L.E. the titre tended to be high during periods of acute illness, but relatively low during remissions.

M. Wilkinson.

Latex-Agglutination Test for Disseminated Lupus Erythematosus. CHRISTIAN, C. L., MENDEZ-BRYAN, R. and LARSON, D. L. (1958). *Proc. Soc. exp. Biol. (N.Y.)*, **98**, 820. 9 refs.

Recent studies by various workers have shown an interaction between the serum of patients with disseminated lupus erythematosus (D.L.E.) and whole nuclei or nucleoprotein, demonstrable by immunofluorescence, complement fixation, or agglutination of nucleoprotein-coated sheep cells. The present paper, from the Presbyterian Hospital (Columbia University), New York, describes how latex particles coated with nucleoprotein from the calf thymus were agglutinated by most D.L.E. sera tested. Because occasional sera, notably from patients with rheumatoid arthritis, agglutinated uncoated latex, all sera which agglutinated nucleoprotein latex were checked against uncoated latex.

It was found that a positive reaction against nucleoprotein-coated latex was given by sera from nineteen out of 24 patients with D.L.E. who had at some time shown a positive L.E.-cell test reaction, and two out of six sera from patients with probable D.L.E. (but a negative L.E.-cell test result). No agglutination occurred with sera from four patients with discoid L.E., fifty with rheumatoid arthritis, or 84 patients with other diseases. However, the sera of three further patients with rheumatoid arthritis and of one patient each with multiple myeloma and chronic renal disease showed agglutination with both uncoated and nucleoprotein-coated latex. It was

further shown that agglutination of nucleoprotein-coated latex was inhibited by previous exposure of a positive D.L.E. serum to deoxyribonucleic acid, but not by exposure to ribonucleic acid, deoxyribose, or histone. In two cases the absorption of positive D.L.E. sera with nucleoprotein-coated latex markedly reduced or abolished their agglutination titre and reversed a positive L.E.-cell test reaction in each case. The authors consider that this is valuable in the diagnosis of D.L.E., and particularly in differentiating it from rheumatoid arthritis.

M. Wilkinson.

On the Interaction of Dead Leucocytic Nuclei, L.E. Factor, and Living Leucocytes in the L.E. Cell Phenomenon. NATHAN, D. J., and SNAPPER, I. (1958). *Blood*, **13**, 883. 6 figs, 12 refs.

In this paper from the Beth-El Hospital, Brooklyn, New York, the authors report some further studies on the mechanism of L.E.-cell formation. Bare leucocyte nuclei were prepared by incubating normal human leucocytes with 0·2 per cent. citric acid solution for 30 minutes at 37° C. The nuclei were then washed with normal saline and incubated with serum from patients with disseminated lupus erythematosus (L.E. serum) for one hour. After rewashing they were incubated for 2 hours with a fresh preparation of buffy coat from the same normal human donor and then examined for L.E. cells. In each of ten experiments with two potent L.E. sera, abundant L.E. cells were seen, whereas in ten control experiments with normal sera, no L.E. cells were found. In all instances the supernatant L.E. serum showed a marked reduction or total loss of L.E.-factor activity after contact with the bare nuclei. This confirms the finding of Miescher and Fauconnet (*Experientia* (*Basel*), 1954, **10**, 252) that the L.E. factor is adsorbed by isolated leucocyte nuclei.

To determine whether intact leucocytes would adsorb the L.E. factor the authors used a suspension of washed normal leucocytes which had been kept at room temperature for 24 hours. These leucocytes were mostly dead but intact, and after incubation with potent L.E. serum only a few L.E. cells resulted. The leucocytes were then separated from the serum by centrifugation and, after further washing, were incubated with fresh normal buffy coat for 2 hours. In none of the five experiments performed was there any further increase in the number of L.E. cells, nor was there any reduction in the L.E.-cell activity of the L.E. serum after its separation from the leucocytes.

These findings seem to support Miescher's opinion that the L.E. factor is an antinuclear auto-antibody with no affinity for the chemically different cytoplasmic nucleic acid. It would appear that viable leucocytes may play some role in L.E.-cell formation in addition to that of phagocytosis, since the bare nuclei did not undergo the swelling and homogenization characteristic of the L.E. phenomenon when they adsorbed L.E. factor, but only when viable leucocytes were subsequently added. The authors suggest that the cytoplasm of the dead leucocyte acts as a barrier between the L.E. factor and the nuclear material which must be breached by viable leucocytes before the L.E. factor can be adsorbed to the nucleus, and that the living leucocytes serve the additional function of transforming nuclei to which L.E. factor has been adsorbed into swollen, homogeneous L.E. bodies.

M. Wilkinson.

State of the Renal Blood Vessels in Rheumatism. (A Comparison of Histological and Angiographic Appearances.) SEROV, V. V. (1958). *Arh. Patol.*, **20**, 27. 8 figs, 32 refs.

Histo-stereoangiographic methods were used [at the Sečenov Medical Institute, Moscow] in a *post mortem* study of the kidneys of 25 patients aged 14 to 60 years who had died of rheumatic heart disease with decompensation and of 25 control subjects, including healthy persons who had died suddenly as a result of trauma. In rheumatism pronounced changes are present in the renal vessels which have a definite relationship to the phase of the rheumatic process. In acute exacerbations of rheumatic fever widespread inflammatory changes with increased vascular permeability are found, mainly in the small arteries in the renal cortex, while during periods of quiescence sclerotic changes are prevalent in the same vessels. The degree of vascular change in the kidneys is directly related to the duration of the disease and the number of acute attacks.

The inflammatory and sclerotic changes in the renal blood vessels which are characteristic of this disease bring about a disturbance of blood flow in part of the renal circulation. A number of compensatory adaptive mechanisms can be demonstrated, mainly consisting in arterio-venous anastomoses and pyramidal collateral vessels. These vessels allow a certain amount of blood to by-pass the cortical circulation, a fact which may play some part in the development of renal disturbances and cardiovascular insufficiency in patients with rheumatic heart disease.—[*From the editorial summary.*]

[The technical details of the method of investigation are not given, and the contrast medium used is not specified. The bibliography is poor, the latest reference from the foreign literature being dated 1938, and the author gives no indication of any acquaintance with Trueta's work or its futher development by others. In itself, however, his work appears to be sound.]

A. Swan.

Use of Latex-Agglutination Reaction in the Diagnosis of Rheumatoid Arthritis. ULLOA, A., GRIFFIN, S. W., HAYES, M. L., and HOLLEY, H. L. (1959). *J. med. Ass. Ala*, **28**, 212. 12 refs.

Clinical Significance of Agglutination Technique in Rheumatoid Arthritis. [In English.] BERKOWITZ, S. S., FINKELSTEIN, A. E., CORCOS, J., STEINBROCKER, O., and LUCE, S. L. (1958). *Arch. interamer. Rheum.*, **1**, 505. 10 refs.

Incidence of the Agglutination Activating Factor in Rheumatoid Arthritis. [In English.] JULKUNEN, H., LAINE, V., KOSKINEN, H.-M., and TILIKAINEN, A. (1958). *Ann. Med. exp. Fenn.*, **36**, 403. 2 figs, 6 refs.

Glutamic-oxalacetic Acid Transaminase (GOT) in Rheumatic Subjects. [In English.] JULKUNEN, H., and RUUTSALO, H.-M. (1958). *Ann. Med. intern. Fenn.*, **47**, 191. 1 fig., 18 refs.

Cryoglobulins in Chronic Lupus Erythematosus. [In English.] CHORAZAK, T. (1958). *Acta derm.-venereol. (Stockh.)*, **38**, 322. 15 refs.

Donaggio's Reaction in Inflammatory Rheumatism. (Réaction de Donaggio et rhumatismes inflammatoires.) BRAUN, M. S. (1959). *Bull. Soc. méd. Hôp. Paris*, Nos. 1 and 2, p. 17. 5 refs.

Comparison of Two Serological Assays of Properdin in Normal Sera and Sera from Patients with Rheumatoid Arthritis and Cancer. [In English.] LAURELL, A.-B. (1959). *Acta path. microbiol. scand.*, **45**, 186. 8 refs.

Behaviour of C-reactive Protein, Serum Glycoproteins, and the Erythrocyte Sedimentation Rate during the Course of Rheumatic Diseases. (Comportamento comparativo della proteina C-reattiva, delle glicoproteine sieriche e della V.E.S. durante il decorso della malattia reumatica.) DI PAOLO, E., and GALLETTI, F. (1958). *G. Clin. med.*, **39**, 1543. 1 fig., 12 refs.

Localization of C-Reactive Protein by Immuno-Electrophoresis. (Localização da proteína C-reativa por imuno-electro-forese.) FERRI, R. G., and COSSERMELLI, W. (1958). *Arch. interamer. Rheum.*, **1**, 493. 3 figs, 12 refs.

Mucoproteins in Inflammatory Rheumatism. (Las mucoproteínas en los reumatismos de base inflamatoria.) OBACH BENACH, J., and BARCELÓ, P. (1958). *Rev. esp. Reum.*, **7**, 664. 8 refs.

ACTH, Cortisone, and Other Steroids

Effectiveness of Antacids in reducing Digestive Disturbances in Patients treated with Prednisone and Prednisolone. BOLAND, E. W., and HEADLEY, N. E. (1958). *Calif. Med.*, **89**, 262. 14 refs.

The authors' preliminary studies with prednisone and prednisolone in the treatment of rheumatoid arthritis indicated that digestive disturbances occurred more frequently in patients treated with these drugs than in those treated with hydrocortisone. Thus, among 109 patients initially treated with hydrocortisone the incidence of digestive complaints was 6·4 per cent., but when these patients were later treated with prednisone or prednisolone the incidence rose to 30 per cent. In the present study of 100 unselected patients with rheumatoid arthritis attending St. Vincent's Hospital, Los Angeles, treatment with prednisone or prednisolone was supplemented therefore by the addition of antacids, 300 mg. dried aluminium hydroxide gel and 50 mg. magnesium trisilicate being given along with each tablet containing 2·5 mg. of the steroids, the period of treatment extending to one year or longer. (Of these patients, 64 had previously been treated with prednisone or prednisolone without antacids for periods varying from 4 to 22 months.)

Of the whole series, eighteen patients developed digestive disturbance; in twelve of these the symptoms were mild and transient, but in six they were persistent and had some of the features of peptic ulcer. Of the 64 patients previously treated without antacids only eleven (17 per cent.) now complained of gastro-intestinal symptoms during combined therapy, whereas previously 24 (38 per cent.) had done so. A diagnosis of peptic ulcer, confirmed radiologically, had been made in nine of the 100 patients before they received therapy. During the administration of the steroids and antacids, seven of these patients had digestive symptoms, compared with eleven of the 91 remaining patients. Digestive disturbance occurred in 12·5 per cent. of patients receiving less than 10 mg. prednisone or prednisolone a day and in 23 per cent. of those receiving 10 mg. or more a day. The incidence of symptoms was higher in those receiving steroid therapy for a longer time, and was also higher in women (20 per cent.) than in men (12 per cent.). Radiological examination of all the patients over a period of one month during the course of the treatment revealed the presence of three active ulcer craters.

The authors conclude that the frequency and severity of digestive symptoms due to prednisone or prednisolone are substantially reduced when these drugs are taken in combination with an antacid preparation, and that the latter may afford some protection against the development of peptic ulcer. *C. E. Quin.*

Protein Metabolism during Corticosteroid Therapy. WEST, H. F. (1958). *Lancet*, **2**, 877. 11 refs.

In this study, which was undertaken at the Centre for the Investigation and Treatment of Rheumatic Diseases, Sheffield, in an attempt to confirm or refute the common assertion that corticosteroid treatment has a protein-catabolic effect, changes in the patient's muscle mass were taken as the index of changes in the body protein store and the daily urinary excretion of creatinine as the index of change in muscle mass. The 24-hour urinary creatinine excretion recorded on numerous occasions was reviewed in respect of nineteen patients (seven men and ten women with rheumatoid arthritis, and two women with ankylosing spondylitis) who had been treated for periods of 6 months to more than 4 years with corticosteroids. In most cases the patients had received a daily intramuscular injection of corticotrophin in a dose sufficient to maintain a daily urinary output of 17-ketogenic steroids or 17-hydroxycorticosteroids of 20 to 30 mg., while the others were given cortisone acetate 50 to 75 mg. daily, or prednisolone 12·5 to 15 mg. daily.

From the fact that of the nineteen patients no fewer than thirteen showed an increase in muscle mass at some time during treatment and only one had consistently shown a loss the author concludes that prolonged corticosteroid therapy is likely to be accompanied by a gain in protein stores rather than a loss, provided that the patient eats normally and can take enough exercise

to avoid the muscular atrophy resulting from disuse. It follows that the often recommended concurrent administration of a protein-anabolic hormone (such as testosterone) is not justified. *Kenneth Stone.*

Neuro-Psychiatric Complications of Treatment with Cortisone and Corticotrophin. NEVZOROVA, T. A. (1958). *Klin. Med.* (*Mosk.*), **39**, 17. 21 refs.

Psychiatric complications occurring during treatment with cortisone and ACTH are not rare and usually appear either at the beginning or at the end of treatment. When they occur at the beginning they are mostly manifested by euphoria, which no doubt is due to the stimulating effect of the hormones, while at the end of treatment they usually take the form of psychoses (such as maniacal or depressive conditions), a sense of fear, epilepsy or status epilepticus, syndromes of disorientation, or an amnesic syndrome. A state of agitation or fear may be a prodromal symptom. The mechanism of these psychiatric symptoms at the end of the treatment is not clear, but it is possible that they may be due to metabolic changes.

For the prevention of these disturbances the following measures are suggested:

(1) Corticoid treatment should always be accompanied by a strict control of potassium and calcium metabolism;

(2) The diet should be poor in chlorides, plenty of vegetables and fruit being given to diminish the intake of sodium chloride.

(3) The intake of preparations containing ascorbic acid and potassium ions, in particular potassium bromide and potassium citrate, must be carefully determined.

(4) The sudden withdrawal of cortisone and ACTH must be avoided at all costs. *H. W. Swann.*

Clinical and Metabolic Effects of 16-alpha-methyl-9-alpha-fluoroprednisolone ("Dexamethasone"). (Effetti clinici e metabolici del 16-alfa metil-9 alfa-fluoroprednisolone o desametasone.) VILLA, L., BALLABIO, C. B., and SALA, G. (1958). *Rheumatismo*, **10**, 127. 4 figs, 5 refs.

The effects of dexamethasone ("Decadron") were studied at the General Medical Clinic of the University of Milan in fifteen patients, of whom ten had rheumatoid arthritis, two rheumatic fever, one chronic gout, one scapulo-humeral periarthritis, and one Paget's disease. In each case the previous requirement of prednisone or of triamcinolone had been carefully evaluated. Dexamethasone was given in daily amounts of 0·5 or 6·0 mg. in three or four divided doses. The clinical effects on the various disease processes were fully comparable to those achieved with the other steroids, showing that dexamethasone is 4·2 to ten (average 7·1) times more active than prednisone and four to ten (average seven) times more active than triamcinolone.

The results of laboratory studies were as follows:

(1) Plasma electrolytes before, during, and after treatment were unaffected, and water retention or potassium loss was not observed.

(2) Diabetogenic effects did not appear in four normal subjects, while in one patient with a diabetic syndrome induced by prednisone and triamcinolone the glycosuria disappeared under treatment with dexamethasone; in another patient with diabetes aggravated by prednisone, triamcinolone, and ACTH there was a distinct improvement in the diabetic state.

(3) Nitrogen metabolism appeared to be slightly increased when dexamethasone was given in high dosage.

(4) Uric acid metabolism was not affected by dexamethasone, although the drug was clinically effective in the one case of gout.

(5) Calcium and phosphorus balance studies (three cases) showed either no effect or only a moderate increase in urinary elimination.

(6) Dexamethasone caused a significant reduction in the urinary excretion of 17-ketosteroids and 17-hydroxysteroids [number of cases not stated], while other hormonal effects included the production of a Cushing-like syndrome.

(7) The number of circulating eosinophil granulocytes fell in cases in which previous treatment had not already influenced the initial count [in an unstated proportion of six cases]. *Max Mayer.*

Peptic Ulcers in Rheumatoid Patients receiving Corticosteroid Therapy. FREIBERG, R. H., KAMMERER, W. H., and RIVELIS, A. L. (1958). *Radiology*, **71**, 542.

X-ray examination of the upper gastro-intestinal tract was carried out on nearly all of 114 patients with rheumatoid arthritis on corticosteroid therapy; 35 of these (31 per cent.) were found to have peptic ulcers. (Of 33 patients with rheumatoid arthritis who were not receiving steroids, only nine (3 per cent.) had ulcers.)

In four cases, the ulcer was known to have existed previously; in the other 31 cases, the ulcers were new ones. In contrast to the normally greater frequency of peptic ulcer in the male, these 35 cases showed a roughly equal sex incidence.

Ten of these patients had no symptoms, and most of the others had only minimal trouble. Nevertheless, four patients had gross ulcer bleeding, and three others persistently positive occult blood reactions in the stools. Six patients had an episode of acute abdominal pain, and three of these were operated upon.

Only five of the ulcers seen on *x* ray were in the duodenum; these were apparently of the usual type. The thirty gastric ulcers had an unusual distribution, being nearly all in the antrum, usually on the lesser curvature. Many of these ulcers were shallow, with slight oedema around, and with a flexible base; pylorospasm and duodenal irritability were not found with these ulcers. No malignant ulcer was found in this series. The character of these ulcers, together with the technical difficulty resulting from the severely crippled state of many of these patients, can make their radiological detection difficult. *B. E. W. Mace.*

Hypercortisonism in Patients with Rheumatoid Arthritis. KEMPER, J. W. (1958). *Tex. St. J. Med.*, **54**, 839. 13 refs.

Peptic Ulcer during Treatment of Rheumatoid Arthritis with Cortisone Derivatives. [In English.] GEDDA, P. O., and MORITZ, U. (1958). *Acta rheum. scand.*, **4**, 249. 17 refs.

Contribution to the Study of Tetanic Crises and Psychiatric Disorders during Adrenocortical Hormone Therapy. (Contribution à l'étude des crises de tétanie et des troubles psychiques survenant au cours de l'hormonothérapie cortico-surrénale.) PIGUET, B. (1958). *Rev. Rhum.*, **25**, 814. 51 refs.

Other General Subjects

Occult Blood in Faeces after Administration of Aspirin. STUBBÉ, L. T. F. L. (1958). *Brit. med. J.*, **2**, 1062. 1 fig., 10 refs.

Simultaneously with the study reported by Lange (*Gastroenterology*, 1957, **33**, 770; *Abstr. Wld Med.*, 1958, **24**, 12) on the effect of salicylic acid on the gastric mucosa the present author was carrying out a similar investigation on 140 patients at the University Hospital, Leiden, and on forty normal subjects, none of whom had any symptoms of gastro-intestinal disease. Aspirin (acetylsalicylic acid) was administered during a period of 20 days, or in some cases for a longer period, in daily doses of 1·5 to 3 g.; during the last 6 days of aspirin medication the diet was kept free from meat and green vegetables, no preparations containing iron were given, the patient was instructed not to brush his teeth, and the stools were tested for occult blood by the benzidine reaction, the strength of the benzidine solution used being approximately 0·75 per cent. The result was regarded as positive if a positive reaction was obtained on three successive stool specimens during the period of aspirin medication with the prescribed diet, provided also that three successive negative reactions were obtained after the cessation of aspirin medication.

Occult loss of blood in the faeces was found in approximately 70 per cent. of the 180 subjects, the results in both patients and controls being similar; further, the results were found to be repeatable in 27 out of 28 cases tested. The incidence of occult blood and the strength of the benzidine reaction were not influenced by the dosage of aspirin nor by the form in which it was administered (as tablets or as a powder suspended in water). After the cessation of aspirin medication the benzidine reaction changed from positive to negative in an average period of 4 to 5 days. When enteric-coated tablets of aspirin were administered to twenty of the subjects giving a positive reaction to ordinary aspirin the reaction had changed from positive to negative in only five cases after 13 days of the new medication. Occult blood was not found in patients who received enteric-coated tablets of sodium salicylate ("entrosalyl"), nor in a group of ten patients who received ordinary tablets of sodium salicylate.

[These results differ from those reported by Alvarez and Summerskill (*Lancet*, 1958, **2**, 920), who, however, used a 0·5 per cent. solution of benzidine, which probably explains the smaller proportion of positive reactions in their series.] *Joseph Parness.*

Status of Phenylbutazone ("Butazolidin") in the Treatment of Rheumatic Disorders. GRAHAM, W. (1958). *Canad. med. Ass. J.*, **79**, 634.

Phenylbutazone was given to 270 patients with rheumatic disorders, who had not made a satisfactory response to salicylates. Acute gouty arthritis responded better to phenylbutazone than any other rheumatic disorder; the drug appeared to be more effective than colchicine (although colchicine, with its specific action, may be of diagnostic value at times), and is probably the best for routine use. The suggested dose is 200 mg. three times daily for 2 days, and then 200-300 mg. daily for one week.

90 per cent. of patients with ankylosing spondylitis responded well to phenylbutazone, and this response could be maintained over a long period, often with quite small doses. The author suggests that this drug could often be used in place of radiotherapy in this condition.

By contrast, only 50 per cent. of patients with rheumatoid arthritis felt that phenylbutazone was a worthwhile drug. When it was effective, however, the side-effects and other complications were less serious than with steroid therapy.

About 60 per cent. of patients with degenerative joint disease obtained significant relief with this drug, but they were naturally rather older, and long-term therapy was more troublesome and hazardous.

Treatment had to be discontinued because of side-effects in 22 patients, of whom thirteen had gastro-intestinal symptoms, five oedema due to salt retention, and three dermatitis. No blood dyscrasias occurred. Major side-effects were seen in six patients, but none was fatal. Minor side-effects occurred in 27 per cent. of the patients. Most of the side-effects appeared between the first and the twelfth week of treatment.

The author considers that a trial of this drug is justified in "rheumatic" patients who do not receive relief from salicylates, and who do not exhibit heart disease, gastric disease, or hypersensitivity in any form. If no response occurs, however, the drug should be withdrawn after one week. Close observation of patients, and prompt withdrawal of the drug if side-effects occur, reduce the dangers of its use to a minimum. *B. E. W. Mace.*

Phenylbutazone (Its Uses and Contraindications). (Phenylbutazon (seine Anwendung und seine Kontraindikationen).) VON RECHENBERG, H. K. (1959). *Praxis*, **48**, 90. 28 refs.

Clinical Trials with Phenylbutazone (Butazolidin) plus Prednisone in Rheumatic Disorders. (Ensayos clínicos con la asociación Butazolidina-Prednisona en las enfermedades reumáticas.) BARCELÓ, P., and SERRA PERALBA, A. (1958). *Arch. interamer. Rheum.*, **1**, 17.

Antibiotics and Antimalarial Drugs in Rheumatology. (Die Anwendung der Antibiotica und Antimalariamittel in der Rheumatologie.) BÖNI, A. (1959). *Schweiz. med. Wschr.*, **89**, 264. 4 refs.

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Co-existence of Joint Symptoms and Non-Suppurative Panniculitis. [In English.] FAJERS, C.-M., and THUNE, S. (1958). *Acta rheum. scand.*, **4**, 286. 5 figs, 24 refs.

Conditioned Vasoconstrictor Reflexes in Rheumatic Subjects. (Bedingte Vasokonstriktionsreflexe beim Rheumatiker.) PÄRTAN, J., and WARUM, F. (1958). *Wien. Z. inn. Med.*, **39**, 503. 5 figs, 21 refs.

Rheumatism and Working Capacity. (Rheuma und Arbeitstätigkeit.) BLUMENCRON, W. (1958). *Int. J. proph. Med.*, **2**, 210.

Cost of Rehabilitation in Rheumatic Disease. ROBINSON, H. S. (1958). *J. chron. Dis.*, **8**, 713. 1 ref.

Lugol's Iodine Reaction in Rheumatic Diseases. (La reacción del Lugol en las afecciones reumáticas.) RUIZ MORENO, A., PAZ, M., and NÁPOLI, L. (1958). *Arch. argent. Reum.*, **21**, 168. 3 refs.

CORRIGENDA

In the Abstract of an article entitled:

Interaction of the Rheumatoid Factor with Antigen-Antibody Complexes and Aggregated Gamma Globulin. EDELMAN, G. M., KUNKEL, H. G., and FRANKLIN, E. C. (1958). *J. exp. Med.*, **108**, 105. 5 figs, 21 refs.

which appeared on p. 79 of the March issue of the *Annals* (1959), volume 18, no. 1, a line was omitted from the original copy prepared by Dr. Harry Coke.

The second paragraph of this Abstract should therefore read as follows:

The isolation of R.F. from euglobulin fractions or precipitates obtained from the serum of four patients with rheumatoid arthritis is described, density gradient zone centrifugation being used to obtain 90 per cent. of the 19-S material. Evidence was obtained that the addition of purified R.F. increased the amount of precipitate formed in systems consisting of ovalbumin, human albumin, and human γ globulin with the corresponding rabbit antibodies, the precipitates being compared by determining their nitrogen content. Furthermore, an additional precipitate occurred on the addition of R.F. to the supernatant fluid removed after precipitation had taken place in the control series, indicating the reaction of R.F. with soluble antigen-antibody complexes. In the zone of excess antibody globulin, where there is no soluble antigen-antibody complex, no precipitation occurred as the result of the addition of R.F. No similar increase in precipitation by R.F. was noted in a horse anti-pneumococcus Type-III system. Heating R.F. to 56° C. for one hour reduced only slightly the potentiation of precipitation in an anti-human-albumin system, and prolonging the reaction time of the antigen-antibody system from 24 hours to 7 days at 4° C. had no significant effect. An approximate linear relationship was established between the nitrogen content of the precipitate produced by the addition of R.F. and the quantity of protein nitrogen in the antibody-antigen system.

Ann. rheum. Dis. (1959), **18**, 173.

A COMPARISON OF PREDNISOLONE WITH ASPIRIN OR OTHER ANALGESICS IN THE TREATMENT OF RHEUMATOID ARTHRITIS

REPORT BY THE JOINT COMMITTEE OF THE MEDICAL RESEARCH COUNCIL AND NUFFIELD FOUNDATION ON CLINICAL TRIALS OF CORTISONE, ACTH, AND OTHER THERAPEUTIC MEASURES IN CHRONIC RHEUMATIC DISEASES*

The results of previous trials conducted by the Joint Committee (1954, 1955, 1957a) showed that there was little to choose between cortisone and aspirin in the long-term management of patients with rheumatoid arthritis, and a similar result was obtained in a trial conducted by the Empire Rheumatism Council (1955, 1957). Since the time of these trials many analogues of cortisone have been introduced, and, of these, prednisone and prednisolone appeared to be particularly suitable for the treatment of rheumatic diseases. Further trials were therefore initiated by the Joint Committee in 1955. In the first of these prednisone was compared with cortisone in the long-term treatment of rheumatoid arthritis. The results of this trial, which have already been published (1957b), showed that for this purpose prednisone was better than cortisone. The present report concerns another trial in which prednisolone was compared with aspirin or other analgesics in the treatment of patients with rheumatoid arthritis.

* MEMBERS OF THE JOINT COMMITTEE: Lord Cohen of Birkenhead (*Chairman*), Prof. E. G. L. Bywaters, Dr. W. S. C. Copeman, Sir Charles Dodds, Dr. J. J. R. Duthie, Prof. A. Bradford Hill, Dr. H. F. West; Prof. J. H. Kellgren (*Medical Secretary*), Mr. J. C. Beavan (*Lay Secretary since* 1957 *in succession to* Mr. W. A. Sanderson).

PARTICIPATING PHYSICIANS: Prof. E. G. L. Bywaters (Postgraduate Medical School of London), Dr. W. S. C. Copeman (West London Hospital Medical School), Dr. J. J. R. Duthie (Rheumatic Unit, Northern General Hospital, Edinburgh), Dr. A. G. S. Hill (Oxford Regional Rheumatic Diseases Research Centre), Prof. J. H. Kellgren (Rheumatism Research Centre, Manchester), Dr. G. D. Kersley (Royal National Hospital for Rheumatic Diseases, Bath), Dr. R. M. Mason (Dept. of Physical Medicine and Regional Rheumatism Centre, London Hospital); Dr. H. F. West (Sheffield Centre for the Investigation and Treatment of Rheumatic Diseases).

STATISTICAL ANALYSIS: Dr. W. J. Martin (Medical Research Council Statistical Research Unit, London School of Hygiene and Tropical Medicine).

Methods and Material

Diagnostic Criteria

The criteria for entry into the trial were similar to those used previously, and patients of either sex between the ages of 17 and 59 years were admitted if they had a rheumatoid type of arthritis of from 3 to 24 months' duration affecting more than three joints with bilateral involvement of hands or feet, ankles or wrists. A sheep cell agglutination test was done on all patients entering the trial, but the results of this test were not included in the criteria for entry.

Treatment

The general management of the patients in terms of rest, splintage, exercise, and physiotherapy was to be that used currently in each participating centre. Within each centre one group of patients received prednisolone in an initial dosage of 20 mg. daily, to be adjusted subsequently on an individual basis to give the maximum therapeutic response obtainable without serious side-effects. To a second group aspirin or other analgesics were given; most patients in this group received aspirin in an initial daily dose of 6·0 g. though seven of the 39 patients received phenylbutazone instead with an initial daily dose of 400 mg. For allocation to one or other group, randomized treatment orders, stratified for sex and for disease duration of under or over 9 months, were prepared for each of the eight participating centres separately.

Assessments

Clinical evaluation and simple laboratory tests such as the erythrocyte sedimentation rate, haemoglobin, and white cell counts were made on entry, and after 4, 8, 12 and 24 weeks and 1, 1½, and 2 years of therapy. Sheep cell agglutination tests were done on entry and after ½, 1, 1½, and 2 years of therapy. *X* rays of the hands and feet were taken on entry and after 1 and 2 years.

The clinical assessment, which was similar to that used in previous trials, included the physician's opinion about the following four characteristics:

(1) Degree of disease activity in four grades.
(2) Patient's general functional capacity in five grades varying from normality (1) to complete crippling (5).
(3) Joint pain and tenderness in four grades.
(4) Joint swelling in four grades.

The strength of grip with each hand was recorded in mm. Hg.

Body weight and blood pressure were recorded.

Certain defined side-effects of therapy, such as dyspepsia, moon face, hirsuties, tinnitus, deafness, changes of mood, etc., were recorded as absent or present, and details of other complications and intercurrent illnesses were also asked for.

Radiographs of the spine and a barium meal were included in the 2-year assessment.

Number of Patients

84 patients entered the trial. Their distribution by sex, disease duration, and treatment group is shown in Table I. One patient died early in the second year, four were lost to follow-up, and two have been excluded from the final analysis, so that the results of 2 years' therapy are compared in 77 patients, of whom 41 were originally allocated to prednisolone and 36 to analgesics.

Deaths and Withdrawals.—Two patients died during the trial. The first died at the time of the 2-year assessment and has therefore been included in the analysis of the clinical and laboratory data. She was a female aged 44 years with a disease duration of 4 months on entry. She was treated with 400 mg. phenylbutazone and 4 g. aspirin during the first year and by aspirin alone during the second year. During the second year she developed pneumonia for which she was admitted to another hospital where she later developed heart failure associated with mitral stenosis and bronchiectasis and she died from this at the end of the second year. The other death was that of a male aged 53 with a disease duration of 8 months on entry. He was treated with aspirin throughout, did badly, and died of heart failure at another hospital at the beginning of the second year. This patient has been excluded from the analysis.

Two female patients, one on prednisolone and one on aspirin, developed complete remission of the arthritis during the early weeks of the trial and could not be traced at follow-up. Neither showed any serological or radiological abnormalities and they may well have had some more benign form of polyarthritis.

Two further patients were lost to follow-up. One was a male of 59 years treated with prednisolone who developed recurrent pericolic abscesses from diverticulitis during the second year. Because of this he was transferred to another hospital where prednisolone was discontinued. The other was a male aged 39 who was treated with phenylbutazone and aspirin. He defaulted at the end of the first year and could not be traced.

The two patients who were followed for 2 years but have been excluded from the analysis were both females allotted to prednisolone, aged 53 and 19 respectively. The first developed an acute psychosis during the first week of therapy and was subsequently treated with aspirin for 2 years and did well. The second developed typical dermatomyositis a few weeks after entry. The sheep cell agglutination test remained negative throughout and the 2-year *x* rays

TABLE I

DISTRIBUTION OF PATIENTS BY SEX AND DURATION OF DISEASE AT ENTRY INTO THE TRIAL
(Figures in brackets represent patients not included in the analysis at 2 years)

Duration of Disease (mths)	Treatment Group	Sex			Total Entered
		Male	Female	Total	
3–8	Analgesics	5 (1)	10 (1)	15 (2)	17
	Prednisolone	8 (1)	7 (3)	15 (4)	19
9–24	Analgesics	10 (1)	11	21 (1)	22
	Prednisolone	9	17	26	26
Total	Analgesics	15 (2)	21 (1)	36 (3)	39
	Prednisolone	17 (1)	24 (3)	41 (4)	45

showed calcification in the soft tissues but no articular erosion. These findings suggest that the original diagnosis may have been incorrect.

Changes of Treatment and Dosage

The mean daily dosage of prednisolone given during the 2 years is shown in Table II. There is a steady fall from 17·4 mg. at Week 4 to 10·0 mg. at 2 years, and only 35 of the 41 patients seen at that time were still receiving prednisolone. Three were taking aspirin instead of prednisolone, one was on corticotrophin instead of prednisolone, and two were not taking any drugs. During the second year an increasing number of patients in this group also took aspirin in one form or another, so that by the end of the year seventeen patients were taking aspirin in addition to prednisolone.

Of the 36 patients who started on analgesics, five had changed to prednisolone and one to cortisone by the end of the second year. At this time twenty were still on aspirin only, seven on phenylbutazone mostly combined with aspirin, and three were taking no tablets of any kind. The dosage of analgesics was also gradually reduced during the 2 years of therapy, but since different preparations were used no mean dosages are shown.

Since most of these changes in therapy only occurred towards the end of the second year they have been disregarded in the Tables of results which show the patients in the treatment groups to which they were originally allocated.

The reason for changing from analgesics to prednisolone was usually inadequate symptomatic control, whereas the abandonment of prednisolone therapy or its partial substitution by aspirin was usually due to complications and side-effects; these will be described in detail later.

TABLE II
DAILY DOSAGE OF PREDNISOLONE

Time of Assessment	Mean Dosage (mg.)	Standard Deviation	Number of Patients
Week 4	17·4	3·74	41
Week 8	16·1	3·92	38
Week 12	15·0	4·04	39
Week 24	13·6	5·03	39
Week 52	12·0	3·48	38
Year 1½	11·2	3·38	36
Year 2	10·0	3·54	35

Results

The general condition of the patients in the two treatment groups as judged by the physician's opinion about disease activity, functional capacity, joint pain or tenderness, and joint swelling are set out in Tables III to VI, in which the results at the various assessment times up to 2 years of treatment are shown. It will be seen that in all these characteristics the two treatment groups were reasonably comparable at the start, though the prednisolone group contained a few more of the severely ill patients. The patients in this group showed, however, a greater early improvement on the average than those in the analgesics group, and this advantage to prednisolone persisted and was still

TABLE III
NUMBER OF PATIENTS WITH GIVEN GRADES* OF DISEASE ACTIVITY

Time of Assessment	Treatment Group	Grade				Died	Total
		0	1	2	3		
Week 0	Analgesics	—	13	21	2	—	36
	Prednisolone	—	9	27	5	—	41
Week 4	Analgesics	1	22	11	2	—	36
	Prednisolone	9	29	3	—	—	41
Week 8	Analgesics	2	17	15	1	—	35
	Prednisolone	14	24	3	—	—	41
Week 12	Analgesics	3	19	10	2	—	34
	Prednisolone	16	21	4	—	—	41
Week 24	Analgesics	4	22	8	1	—	35
	Prednisolone	10	22	8	1	—	41
Week 52	Analgesics	4	18	11	1	—	34
	Prednisolone	10	25	5	—	—	40
Year 1½	Analgesics	3	18	12	1	—	34
	Prednisolone	6	27	8	—	—	41
Year 2	Analgesics	4	22	9	—	1	36
	Prednisolone	5	30	6	—	—	41

* *Grade:* 0 = None 1 = Slight 2 = Moderate 3 = Severe

TABLE IV

NUMBER OF PATIENTS WITH GIVEN GRADES* OF FUNCTIONAL CAPACITY

Time of Assessment	Treatment Group	Grade					Died	Total
		1	2	3	4	5		
Week 0	Analgesics	—	8	24	3	1	—	36
	Prednisolone	—	11	16	9	5	—	41
Week 4	Analgesics	1	21	13	—	1	—	36
	Prednisolone	8	22	8	2	1	—	41
Week 8	Analgesics	3	17	14	—	1	—	35
	Prednisolone	16	20	3	1	1	—	41
Week 12	Analgesics	4	18	11	1	—	—	34
	Prednisolone	20	16	3	1	1	—	41
Week 24	Analgesics	5	23	5	2	—	—	35
	Prednisolone	19	16	3	1	2	—	41
Week 52	Analgesics	10	18	6	—	—	—	34
	Prednisolone	22	14	3	—	1	—	40
Year 1½	Analgesics	6	21	6	1	—	—	34
	Prednisolone	17	22	2	—	—	—	41
Year 2	Analgesics	9	18	7	—	1	1	36
	Prednisolone	19	18	3	1	—	—	41

* *Grade:* 1 = Fully employed or employable in normal work and able to undertake normal physical recreation.
2 = Fully employed in special work after vocational training, or doing light or part-time work in normal occupation. Limitation in amount of physical recreation. Housewives, all except the heaviest housework. In-patients, in hospital for investigation only.
3 = Not employed or employable. Very limited physical activity and little or no capacity for physical recreation. Housewives, light housework and/or limited shopping only. In-patients in hospital for treatment but up and about in ward.
4 = Confined to hospital, house, or wheelchair, but able to look after themselves in the essentials of life. In-patients in hospital for treatment sitting up but not getting about.
5 = Confined to bed and unable to look after themselves. In-patients on complete rest in bed.

TABLE V

NUMBER OF PATIENTS WITH GIVEN GRADES* OF JOINT PAIN OR TENDERNESS

Time of Assessment	Treatment Group	Grade				Died	Total
		0	1	2	3		
Week 0	Analgesics	—	11	21	4	—	36
	Prednisolone	—	13	19	9	—	41
Week 4	Analgesics	3	17	15	1	—	36
	Prednisolone	19	18	3	1	—	41
Week 8	Analgesics	4	16	13	2	—	35
	Prednisolone	20	17	4	—	—	41
Week 12	Analgesics	5	19	7	3	—	34
	Prednisolone	20	18	3	—	—	41
Week 24	Analgesics	3	23	7	2	—	35
	Prednisolone	12	21	7	1	—	41
Week 52	Analgesics	4	22	5	3	—	34
	Prednisolone	12	21	7	—	—	40
Year 1½	Analgesics	2	19	12	1	—	34
	Prednisolone	12	19	9	—	—	40
Year 2	Analgesics	3	23	8	1	1	36
	Prednisolone	9	22	10	—	—	41

* *Grade:* 0 = None 1 = Slight 2 = Moderate 3 = Severe

present though less marked by the end of the second year.

The changes in strength of grip and in the results of laboratory tests such as the erythrocyte sedimentation rate, haemoglobin, and white cell count are set out in Table VII (opposite), which also includes body weight. The mean value for each characteristoc at each assessment time is given.

The patients receiving prednisolone showed a large improvement in strength of grip at Week 4

TABLE VI

NUMBER OF PATIENTS WITH GIVEN GRADES* OF JOINT SWELLING

Time of Assessment	Treatment Group	Grade				Died	Total
		0	1	2	3		
Week 0	Analgesics	1	14	20	1	—	36
	Prednisolone	1	20	18	2	—	41
Week 4	Analgesics	2	25	8	1	—	36
	Prednisolone	19	19	3	—	—	41
Week 8	Analgesics	5	18	11	1	—	35
	Prednisolone	19	20	2	—	—	41
Week 12	Analgesics	6	19	9	—	—	34
	Prednisolone	17	22	2	—	—	41
Week 24	Analgesics	6	21	8	—	—	35
	Prednisolone	11	23	6	1	—	41
Week 52	Analgesics	5	19	10	—	—	34
	Prednisolone	12	20	8	—	—	40
Year 1½	Analgesics	2	23	9	—	—	34
	Prednisolone	12	20	8	—	—	40
Year	Analgesics	5	18	12	—	1	36
	Prednisolone	16	18	7	—	—	41

* *Grade:* 0 = None 1 = Slight 2 = Moderate 3 = Severe

TABLE VII

AVERAGE MEASUREMENTS OF VARIOUS CHARACTERISTICS

Time of Assessment	Treatment Group	Strength of Grip (mm. Hg)		Erythrocyte Sedimentation Rate (mm./hr)	Hb (g. per cent.)	White Cell Count	Weight (lb.)
		Left	Right				
Week 0	Analgesics	133	131	36	13·1	8,900	136
	Prednisolone	119	110	41	12·7	8,300	141
Week 4	Analgesics	152	155	32	12·9	8,100	137
	Prednisolone	209	217	14	14·1	11,200	142
Week 8	Analgesics	152	163	34	13·1	8,000	138
	Prednisolone	222	222	14	14·6	10,600	146
Week 12	Analgesics	151	160	27	13·2	8,100	138
	Prednisolone	225	226	18	14·4	10,600	149
Week 24	Analgesics	159	175	23	13·8	7 200	136
	Prednisolone	206	210	21	14·3	9,800	150
Week 52	Analgesics	154	166	31	13·1	8,000	137
	Prednisolone	203	210	22	13·8	11,000	150
Year 1½	Analgesics	144	157	32	12·8	7,500	136
	Prednisolone	206	206	22	13·6	9,000	149
Year 2	Analgesics	152	163	29	13·2	8,500	138
	Prednisolone	195	199	25	13·7	9,500	146

and a further small improvement at Week 8; by 6 months a slight decrease commenced and the values at the end of the second year, though much above the starting point, were slightly below those of Week 4. In the analgesics group there was only a slight improvement throughout the 2 years. At 2 years the improvement in the prednisolone group was still significant ($p < 0{\cdot}001$), but that in the analgesics group was not.

The erythrocyte sedimentation rate showed similar changes, the prednisolone group recording a marked fall at Week 4 followed by a gradual rise and the improvement at 2 years being still significant ($p < 0{\cdot}01$). The analgesics group showed no significant improvement.

The haemoglobin values showed a similar early rise and later slight decline in the prednisolone group with a significant remaining improvement at 2 years ($p < 0{\cdot}01$), but no such improvement occurred in the analgesics group.

The total white cell count rose at Week 4 in the patients receiving prednisolone and then declined,

but the 2-year figure was not significantly higher than that recorded initially in either group.

Thus, in the prednisolone group, all these characteristics showed marked early improvement which later became less but, with the exception of the white cell count, this improvement was still significant at 2 years, whereas there was no significant improvement in the analgesics group.

Body weight rose steadily in the prednisolone group during the first 6 months of therapy and during the second 6 months the patients in the prednisolone group were on average 13-14 lb. heavier than the patients in the analgesics group who had shown no change in body weight. During the second year the patients in the prednisolone group lost weight, so that after 2 years' treatment their average weight was only 8 lb. greater than that of the patients in the analgesics group.

X-Ray Changes

The *x* rays of the hands and feet were all read at one time by a single observer (J. H. Kellgren) who was unaware of the treatment given, and the overall gradings for rheumatoid change, which include articular erosion, subluxations, and osteoporosis, are shown in Table VIII which gives the rheumatoid gradings of the initial, one-year, and two-year films. Initially the two groups were similar, but the patients treated by analgesics showed a steady increase in the more marked changes. Thus the number of films in this group showing only doubtful changes or none declined from eighteen to five for the hands and from sixteen to seven for the feet, whereas the number of films showing moderate or severe changes increased from six to seventeen for the hands and from nine to eighteen for the feet. In the prednisolone group the increase in severity was much less; the number of films showing only doubtful changes or none declined from 23 to seventeen for the hands and from seventeen to fifteen for the feet, and the number showing moderate or severe changes increased from five to eight for the hands and from ten to twelve for the feet. The significance values in the analgesics group for the differences between the rheumatoid gradings of the initial and the 2-year films of the hands and feet are $p < 0{\cdot}001$ and $p < 0{\cdot}02$ respectively, whereas in the prednisolone group the differences, though in the same direction, are not formally significant. In addition to these gradings of severity the degree of improvement or deterioration was also recorded, since minor degrees of improvement or deterioration, though definite enough to record with confidence, may not always be sufficient to alter the overall grading for severity, and useful minor differences may thus be missed. The numbers of films showing improvement, deterioration, or no change in the two treatment groups are shown in Table IX (opposite). The differences in distribution between the two treatment groups at 2 years has a significance of $p < 0{\cdot}03$ for the hand films and $p < 0{\cdot}0001$ for the foot films.

Improvement in the radiological appearances, such as healing of erosions and increase of bone density, was observed in a few films in both treatment groups. Thus, at the end of 2 years, three of 35 hand films and four of 34 foot films from the analgesics group, and four of 41 hand films and seven of 41 foot films from the prednisolone group showed improvement when compared with the films taken on entry into the trial, but the main difference

TABLE VIII

GRADINGS BY OBSERVER I OF RADIOLOGICAL CHANGES OF RHEUMATOID ARTHRITIS IN FILMS OF HANDS AND FEET

Films	Time of Assessment	Treatment Group	Grade					
			0	1	2	3	4	Total
Hands	Initial	Analgesics	13	5	11	5	1	35*
		Prednisolone	15	8	13	4	1	41
	Year 1	Analgesics	7	3	15	7	3	35
		Prednisolone	13	6	16	4	2	41
	Year 2	Analgesics	4	1	13	11	6	35
		Prednisolone	9	8	16	4	4	41
Feet	Initial	Analgesics	10	6	9	8	1	34
		Prednisolone	10	7	14	9	1	41
	Year 1	Analgesics	7	4	13	9	2	35
		Prednisolone	10	6	12	13	0	41
	Year 2	Analgesics	5	2	10	14	4	35
		Prednisolone	11	4	14	9	3	41

Grade: 0 = None 1 = Doubtful 2 = Slight 3 = Moderate 4 = Severe

* The patient who died at the end of the second year is not included in this Table or in Tables IX, X, and XV.

TABLE IX

CHANGES OF *X*-RAY APPEARANCES IN COMPARISON WITH INITIAL FILMS RECORDED BY OBSERVER I

Films	Time of Assessment	Treatment Group	Changes in *X*-ray Appearances			
			Deterioration	No Change	Improvement	Total
Hands	Year 1	Analgesics	17	17	1	35
		Prednisolone	7	30	4	41
	Year 2	Analgesics	26	6	3	35
		Prednisolone	17	20	4	41
Feet	Year 1	Analgesics	15	15	4	34
		Prednisolone	5	26	10	41
	Year 2	Analgesics	24	6	4	34
		Prednisolone	4	30	7	41

is the lack of radiological deterioration in the prednisolone group, especially in the feet.

Examples of the type of improvement or deterioration noted are shown in Figs 1 to 3; deterioration

(*a*) (*b*)

Fig. 1.—*X* ray of right hand (*a*) at the start and (*b*) after 2 years of treatment, illustrating the greatest degree of deterioration observed in the trial (Grade 0 to 4). This patient was treated with prednisolone initially, and with corticotrophin during the second year.

(*a*) (*b*)

Fig. 2.—The greatest degree of improvement observed in the trial (*a*) in the wrists (Grade 2 to 1) and (*b*) in the feet (Grade 3 to 2).The initial film is above, the 2-year film below. The hands and feet are from two separate patients, both of whom were treated with prednisolone throughout the 2 years.

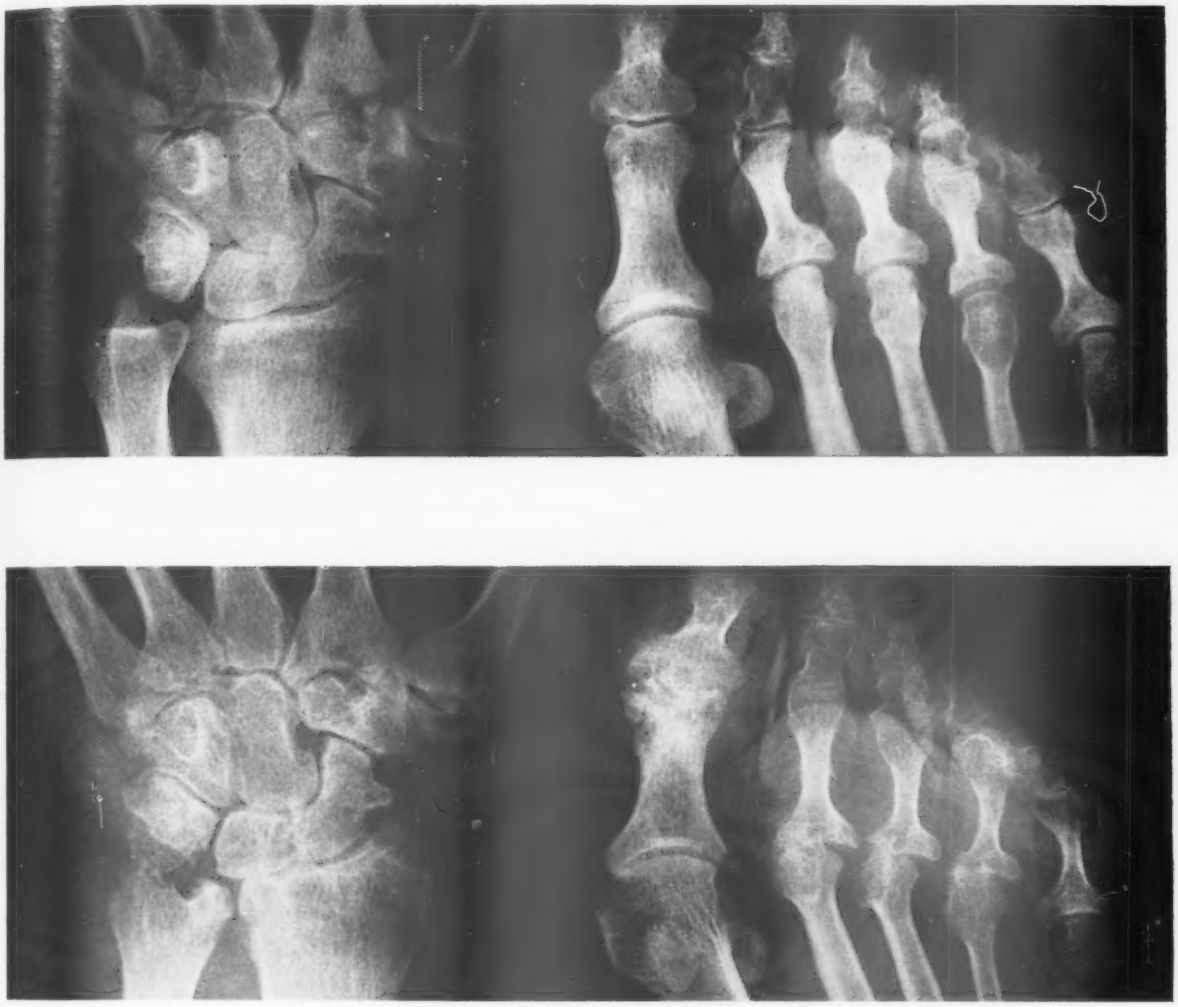
was sometimes pronounced, whereas improvement with actual healing of erosions and recovery of osteoporosis was less striking.

The initial and first year films were also read in a similar way by three other observers (J. J. R. Duthie, H. F. West, and R. M. Mason). Though the criteria for grading varied widely between one observer and another, all noted the same order of difference between the patients treated with analgesics and those receiving prednisolone.

The radiological findings thus reveal a definite advantage to prednisolone, in that during the 2 years of the trial patients receiving prednisolone showed significantly less increase in destructive joint changes than did those treated with analgesics.

Results of Sheep Cell Agglutination Tests

In making the sheep cell agglutination tests somewhat different techniques were used by the participating centres. Details of the methods used are given in the Appendix. Because of these differences in technique, direct comparison of agglutinating titres between one centre and another cannot be made. However, the minimal positive titre used by each centre has been taken as zero and dilutions above and below this have been scored as +1, +2, etc., and −1, −2, etc. The results so obtained are set out in Table X (opposite), to permit some comparison of the two treatment groups. This method of comparing the treatment groups seems justified, since approximately equal numbers of patients in each group were tested by each of the different methods, and it is the changes in agglutinating titre during the course of the trial that are the main interest. At the start of the trial the two treatment groups were similar, although there were somewhat fewer patients with high agglutinating titres in the prednisolone group. The distribution



(*a*) (*b*)

Fig. 3.—Typical examples of moderate deterioration (*a*) in the hands (Grade 1 to 3) and (*b*) in the feet (Grade 3 to 4). The initial film is above, the 2-year film below. Both hands and feet are from the same patient, who was treated with aspirin throughout.

TABLE X

RESULTS OF SHEEP-CELL AGGLUTINATION TESTS*

Time of Assessment	Treatment Group	Results of Sheep Cell Agglutination Tests							Total Negative and Positive
		Negative			Positive				
		−5 to −3	−2 to −1	Total	0 to +1	+2 to +3	+4 to +7	Total	
Initial	Analgesics	6	6	12	8	10	5	23	35
	Prednisolone	5	8	13	14	11	3	28	41
Year 1	Analgesics	11	4	15	7	8	5	20	35
	Prednisolone	9	7	16	6	12	7	25	41
Year 2	Analgesics	5	9	14	9	7	5	21	35
	Prednisolone	6	6	12	5	12	12	29	41

* Based on minimal positive titre = 0, with deviations above and below in numbers of tubes showing agglutination.

of positive and negative tests was almost identical: 23 to 12 in the analgesics group and 28 to 13 in the prednisolone group. After 2 years of therapy the proportions of positive and negative tests had only changed slightly, being 21 to 14 in the analgesics group and 29 to 12 in the prednisolone group. On the other hand, in the prednisolone group, there was a decline in the number of patients giving borderline positive tests from fourteen to five and an increase in those with high agglutinating titres from three to twelve. This change in the distribution of titres within the group of patients with positive tests treated with prednisolone is significant ($p < 0{\cdot}003$). No such systematic change occurred in the sera of patients in the analgesics group in which the distribution of titres amongst those giving positive tests at the end of 2 years was similar to that recorded initially ($p \sim 0{\cdot}4$).

Thus, in the present trial, the agglutinating titres have behaved differently from all the other characteristics recorded: The patients treated with prednisolone show greater improvement in both the clinical and radiological signs of arthritis while at the same time showing a general rise in agglutinating titres amongst those with positive tests.

Complications and Side-Effects

The incidence of the defined side-effects of therapy listed on the record form is shown in Table XI. These were mainly of a minor character and require no comment.

The changes in blood pressure are shown in Table XII. There was a greater tendency for the blood pressure to rise in the prednisolone group, but hypertension did not become a therapeutic problem in any patient during the period of the trial.

TABLE XII

BLOOD PRESSURE

Time of Assessment	Treatment Group	Number of Patients with	
		Systolic Recordings of 160 mm. and over	Diastolic Recordings of 90 mm. and over
Week 0 ..	Analgesics	6	6
	Prednisolone	7	12
Week 4 ..	Analgesics	4	8
	Prednisolone	5	14
Week 8 ..	Analgesics	4	6
	Prednisolone	6	16
Week 12 ..	Analgesics	4	8
	Prednisolone	8	17
Week 24 ..	Analgesics	5	6
	Prednisolone	8	17
Week 52 ..	Analgesics	4	8
	Prednisolone	9	19
Year 1½ ..	Analgesics	5	10
	Prednisolone	12	19
Year 2 ..	Analgesics	6	14
	Prednisolone	12	23

There were a number of major complications and intercurrent illnesses which may have been related

TABLE XI

NUMBER OF PATIENTS WITH GIVEN SIDE-EFFECTS

Time of Assessment	Treatment Group	Side-Effects							
		Tinnitus or Deafness	Dyspepsia	Moonface	Acne	Hirsuties	Oedema	Euphoria	Depression
Week 0	Analgesics	1	2	—	—	1	1	—	5
	Prednisolone	2	3	—	—	—	2	1	4
Week 4	Analgesics	11	12	—	1	2	1	—	5
	Prednisolone	2	4	7	1	—	—	2	—
Week 8	Analgesics	7	9	—	1	—	2	—	3
	Prednisolone	1	2	20	2	—	2	1	1
Week 12	Analgesics	8	5	—	2	—	1	1	2
	Prednisolone	1	10	20	2	1	1	1	—
Week 24	Analgesics	9	7	—	1	1	1	—	—
	Prednisolone	1	9	27	4	2	—	1	1
Week 52	Analgesics	8	7	—	—	1	3	—	—
	Prednisolone	2	6	24	2	4	1	1	—
Year 1½	Analgesics	4	6	1*	—	—	5	—	1
	Prednisolone	—	9	22	1	3	4	2	3
Year 2	Analgesics	1	7	4*	—	1	2	—	—
	Prednisolone	2	8	14	3	2	2	3	2

* These patients changed to cortisone or prednisolone during the trial.

to therapy. The major complications summarized in Table XIII will now be considered in detail.

TABLE XIII

MAJOR COMPLICATIONS AND INTERCURRENT ILLNESSES

Disease	Treatment Group	
	Analgesics	Prednisolone
Psychosis	0	2
Clinical Presentation of Peptic Ulcer during Trial	0	3
Major Intercurrent Infections	3	4
Ecchymosis	1	3
Miscarriage	0	1
Amenorrhoea	0	1
Glycosuria	0	1
Cardiac Infarct	0	1
Insomnia	0	1
Thrombophlebitis	1	1
Herpes Zoster	1	1
Leg Ulcer	1	0
Arteropathy	1	0
Severe Diarrhoea	1	0

Two patients developed a psychosis while on prednisolone therapy. One was a female aged 53 years, who was given 20 mg. prednisolone daily. She developed an acute psychosis on the fourth day of therapy, but recovered rapidly when the treatment was changed to aspirin. This patient was followed for 2 years and did well, but was not included in the analysis. The other was a male aged 59 years who was given 20 mg. prednisolone for 3 months and then developed attacks of panic. The dosage was reduced to 5-10 mg., but he became more disturbed, and by the time of the 2-year assessment he was in a mental hospital as a voluntary patient. No patient receiving analgesics developed psychosis.

Two patients on prednisolone developed bleeding peptic ulcers. One male, aged 39, given 20 mg. prednisolone for over 6 months, developed dyspepsia for the first time and after a few weeks had a severe uncontrollable melaena for which emergency gastrectomy was done at another hospital, where the prednisolone was stopped. Following this, he became extremely ill with febrile rheumatoid disease which could only be controlled by corticotrophin therapy in high dosage. He had a second continuing melaena from a stomal erosion which had to be undersewn. He also had staphylococcal septicaemia and multiple pyarthrosis, but finally recovered enough to leave hospital. The other patient with melaena was a male aged 55 who was given 20-25 mg. prednisolone daily for 6 months when he developed an ulcer type dyspepsia for the first time. A barium meal at that time was normal and the prednisolone dose was reduced to 17·6 mg. supplemented by 4 g. aspirin, but 2 months later he had a melaena and a barium meal showed duodenal ulcer. Prednisolone was gradually withdrawn and aspirin therapy continued, but dyspepsia persisted and the ulcer did not heal during the following 6 months, and after a second melaena a gastrectomy was performed. He was subsequently treated successfully with enteric-coated salicylate. No patient in the analgesics group had an overt gastro-intestinal haemorrhage, though it must be noted that one of the episodes of melaena reported above occurred at a time when the patient was on aspirin only. Another male patient, who received prednisolone in a dosage of 20 mg. daily during the first year, developed ulcer type dyspepsia for the first time during the second year of therapy while receiving 15 mg. prednisolone daily. A barium meal revealed a large gastric ulcer.

Major episodes of infection were reported in seven patients, four in the prednisolone group and three in the analgesics group. Those on prednisolone included the case of staphylococcal septicaemia and the case of peritonitis and pericolic abscesses already described plus one case of cholecystitis and one episode of pleurisy. The infections in the analgesics group included the patient with pneumonia who later died of heart failure and bronchiectasis who has already been described, plus one case of pleural effusion followed by spontaneous pneumothorax and empyema, and an episode of pneumonia in a patient with chronic bronchitis. Thus severe infection appears to have occurred with similar frequency in both treatment groups.

The following were reported once only in patients receiving prednisolone: miscarriage, amenorrhoea, cardiac infarct, glycosuria, thrombophlebitis, herpes zoster, and insomnia. Three patients were reported to have ecchymosis. Amongst the patients receiving analgesics there were also single reports of thrombophlebitis with arteropathy, varicose ulceration, severe diarrhoea, herpes zoster, and ecchymosis.

The main difference as regards complications appeared to be the cases of psychosis and gastro-intestinal bleeding occurring in the prednisolone group, but the numbers are far too small for statistical significance.

Since peptic ulceration and osteoporosis have been regarded as major side-effects of prednisolone therapy, a routine barium meal and spinal *x* rays were included in the 2-year assessment. The results are summarized in Tables XIV and XV (overleaf).

The withdrawals are the two patients excluded from the trial because of early changes of treatment and incorrect diagnosis who both had barium meals at the 2-year assessment. The patient who had prednisolone for 3 days and aspirin for 2 years was reported as having appearances suggestive of

TABLE XIV

EVIDENCE OF PEPTIC ULCERATION AT 2-YEAR ASSESSMENT

Treatment Group	Barium Meals	Evidence of Ulceration				Other	Normal
		Gastrectomy	Duodenal	Gastric	Total		
Analgesics	34	1*	0	0	1	1	32
Prednisolone	40	2	2	2	6	2	32
Withdrawals	2	0	1	0	1	0	1
Total	76	3	3	2	8	3	65

* This gastrectomy was done before entry into the trial.

TABLE XV

SPINAL *X*-RAY CHANGES AFTER 2 YEARS' TREATMENT

Characteristic	Treatment Group	Grade				
		0	1	2	3	Total
Osteoporosis	Analgesics	16	10	1	1	28
	Prednisolone	13	6	13	—	32
Expansion of Disks	Analgesics	23	4	1	—	28
	Prednisolone	25	6	1	—	32
Collapsed or Crushed Vertebrae ..	Analgesics	21	6	—	1	28
	Prednisolone	26	4	2	—	32

Grade: 0 = None 1 = Doubtful 2 = Slight 3 = Moderate

One centre did not take lateral films.

duodenal ulceration, and the patient who had been treated with prednisolone throughout was reported as showing no abnormality in the barium meal.

The radiologists' reports given in the Appendix show that only two of the ulcers were regarded as definite active ulcers at the time of the examination, two duodenal ulcers were reported as healed, and one gastric ulcer was doubtful. Only one of the five patients with radiologically demonstrated ulcer was reported to have dyspepsia, though all the patients who had had gastrectomies had suffered from dyspepsia before their operations and one still had dyspepsia at the 2-year assessment. In contrast to this, there were fourteen additional patients reported to have dyspepsia at the 2-year follow-up in whom no radiological evidence of ulcer was reported.

The most striking feature of Table XIV is the absence of active peptic ulceration amongst the 34 patients in the analgesics group. This is not surprising since patients known to have peptic ulceration would not have been entered for the trial. The barium meal also revealed no abnormality in 32 of the forty patients in the prednisolone group, but some evidence of peptic ulceration was noted in six (15 per cent.). This may be compared with reported ulcer rates ranging from 31 per cent. (Kammerer, Freiberger, and Rivelis, 1958) to 5·3 per cent. (Henderson, 1955) in patients with rheumatic disease treated with corticosteroids.

Of the total 76 patients investigated at the end of 2 years' therapy, eight showed some evidence of past or present peptic ulceration. This figure corresponds closely to the 10 per cent. prevalence in the general population quoted by Kirsner, Kassriel, and Palmer (1956). Even if we bear in mind the facts that all the patients in the trial were under 60 years of age on entry and that only 32 of these were males, the prevalence of peptic ulceration still resembles that reported by Avery Jones (1957) for autopsy findings in coroners' cases.

On the other hand, serious clinical manifestations of peptic ulcer developed for the first time during the 2 years of the trial in three of the seventeen men in the prednisolone group, whereas Avery Jones reports an estimated incidence of 3·2 per 1,000 man years. Furthermore, the three men who developed ulcers during treatment had all received prednisolone in a daily dose of 20 mg. or more for over 3 months, a dosage substantially higher than that given to most patients in the trial. Indeed, this order of dosage was given to only eight patients and of these four had evidence of ulcer and a fifth developed psychosis so that the question of dosage may be crucial.

The films of the lumbar spine were read by Obser-

ver 1. The results are shown in Table XV. Lateral views of the spine were not taken at one centre so that only sixty films were available for study. All that can be said is that these films did not reveal any significant incidence of disk expansion or vertebral collapse in either treatment group. Although more films from the prednisolone group were recorded as showing slight degrees of osteoporosis, the difficulties of estimating osteoporosis in spinal films are great.

Discussion

In the treatment of rheumatoid arthritis short-term improvement can be obtained by giving corticosteroids in high dosage, but the toxic side-effects of steroid therapy increase with the duration of treatment so that when this is prolonged over years the acceptable dosage ceiling becomes severely restricted and the benefits of treatment are proportionately reduced. This emerged clearly from long-term trials in which cortisone did not prove to be superior to aspirin in the treatment of rheumatoid arthritis.

The introduction of more potent analogues with less effect on body electrolytes gave greater promise of success and in the controlled trials conducted by the Joint Committee prednisone has been shown to be superior to cortisone, and prednisolone superior to aspirin or other analgesics in the treatment of rheumatoid arthritis over a 2-year period.

The findings in the present trial are of special interest. The one- and two-year radiographs of the hands and feet more often revealed a distinct increase of erosive joint damage in the patients treated with analgesics than in the patients treated with prednisolone in whom there was much less progression of the joint disease. On the other hand, in the group treated with prednisolone there was in a number of patients a rise in the sheep cell agglutination titres during the two years of therapy, whereas in the patients treated with analgesics there was more often a fall in titre. This is an unexpected finding since, in a previous study (Kellgren, 1957), there was a positive correlation between high titres in the sheep cell agglutination test and the development of articular erosions. This association was much less apparent in the prednisolone-treated patients in this trial and this raises the interesting possibility that the process responsible for joint erosion may not be identical with that producing the rheumatoid serum factor and that prednisolone therapy may suppress the former while enhancing the latter.

In the treatment of rheumatoid arthritis with prednisolone as with all corticosteroids the question of dosage is crucial. After 2 years of therapy the mean dosage in this trial was 10 mg. daily, which is still above the maximum of 9 mg. for men and 5 mg. for menopausal women recommended by Slocumb, Polley, and Ward (1957). Of the eight patients in the trial who received 20 mg. prednisolone daily over 3 months, four had evidence of peptic ulceration and a fifth developed psychosis—a proportion of serious complications which is clearly unacceptable, and this high incidence of complications with high dosage accords with the experience of others (Howell and Ragan, 1956; Black, Yielding, and Bunim, 1957).

Conclusions

From the results of this trial it may be concluded that the administration of prednisolone instead of, or in addition to, analgesics, such as aspirin, to certain patients with rheumatoid arthritis for a period of 2 years will, on average, improve their functional capacity and general well-being and reduce the incidence of erosive joint damage; but more patients are likely to show a rise in sheep cell agglutinating titre, and the significance, if any, for the patients' future is not yet known.

If the daily dose of prednisolone approaches 20 mg., undesirable side-effects are likely to occur and the highest acceptable daily dose for long-term therapy is probably in the region of 10 mg.

Summary

(1) In a controlled therapeutic trial prednisolone has been compared with aspirin or other analgesics in the treatment of rheumatoid arthritis.

(2) Eight centres participated and 84 patients entered the trial. A few patients defaulted, died, or were withdrawn from the trial, so that the results after 2 years' treatment are based on the analysis of 77 patients, of whom 41 were originally allocated to prednisolone and 36 to analgesics.

(3) The patients treated with prednisolone showed an early significant improvement in both clinical and laboratory indices of inflammatory polyarthritis and this improvement, though less, was still present to a significant extent at the end of 2 years.

(4) In the group of patients treated with analgesics the frequency of radiological signs of erosive joint disease in the hands and feet increased significantly over the 2 years, whereas there was no significant change in the group treated with prednisolone.

(5) In many patients treated with prednisolone the agglutinating titre in the sheep cell test rose

during the 2 years of treatment, whereas such a rise occurred in only a few patients treated with analgesics.

(6) Two patients treated with analgesics died of heart failure. Five patients treated with prednisolone developed major complications (two cases of psychosis and three of peptic ulceration). These major complications all occurred in patients receiving a daily dose of 20 mg. or more of prednisolone. Patients receiving prednisolone also gained weight, and showed some rise in blood pressure and a tendency to mooning of the face. During the trial the mean daily dose of prednisolone was gradually reduced from 17·4 to 10·0 mg. and more than half the patients on prednisolone were also receiving aspirin or other analgesics. It is concluded that the optimal daily dose for long-term therapy in the average case of rheumatoid arthritis is not more than 10 mg.

The Committee are indebted to Boots Pure Drug Company and to Upjohn of England for the generous provision of initial supplies of prednisolone for this trial.

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APPENDIX

Serological Methods used for Estimating the Rheumatoid Serum Factor

The following centres used some form of sheep cell agglutination test:

London Hospital: Original Rose-Waaler method (Rose, Ragan, Pearce, and Lipman, 1948) during Year 1, and Ball's method (Ball, 1950) using 18-hour readings during Year 2.

Manchester Royal Infirmary and Edgar Allen Treatment Centre, Sheffield: Ball's method using 18-hour readings (Ball, 1950; Kellgren and Ball, 1959).

Northern General Hospital, Edinburgh: Modification of Ball's method using 18-hour readings in which haemagglutination plates are substituted for tubes (Duthie, Brown, Knox, and Thompson, 1957).

Postgraduate Medical School, London: Modification of original Rose-Waaler method as described by Scott (1952).

Stoke Mandeville Hospital, Aylesbury, Bucks.: Greenbury's method (Greenbury, 1957).

One centre used a human cell agglutination system:

Royal National Hospital for Rheumatic Diseases, Bath: Method described by Gibson and Ling (1956).

Radiologists' Reports on Barium Meals recording Abnormalities other than Gastrectomy

Patients on Analgesics

Male, aged 29 on Entry	"Generalized thickening of the gastric rugae with gastritis but no evidence of gastric or duodenal ulcer or neoplasm."

Patients on Prednisolone

Male, aged 51 on Entry	"No lesion found in the oesophagus. There is a very coarse gastric rugal pattern with a large gastric ulcer on the posterior wall towards the lesser curve. Whilst this may well be a simple ulcer a neoplasm cannot be excluded. No duodenal ulcer detected." *5 weeks later:* "Gastroscopy showed a shallow healing benign ulcer measuring ½ cm. in diameter on the posterior wall towards the lesser curve about 1½ in. from the pars angularis. There was no evidence of neoplasm, haemorrhage or abnormal mucus."
Female, aged 41 on Entry	"No abnormality seen in the oesophagus or stomach. Duodenum—the cap is deformed and there is an ulcer crater present. This was not tender."
Male, aged 52 on Entry	"Barium flowed normally down the oesophagus. No abnormality detected in his stomach. The duodenal cap was deformed. However, as the mucosa of the duodenal cap appears normal and there is no excess resting secretion, the probabilities are that these deformities are due to old and healed ulceration."

FEMALE, AGED 25 ON ENTRY	"There is a slight irregularity on the posterior wall between the fundus and body of the stomach. I cannot exclude a shallow ulcer there, but it is doubtful."
FEMALE, AGED 51 ON ENTRY	"The oesophagus is normal except that there is a tendency to dilation of the ampulla phrenica. No hiatal herniation. The stomach is of normal 'J' type and shows good tone and regular peristalsis. In the erect position there is a small projection on the lesser curve at about the site of insertion of the ligament of Treitz. I do not think this is an ulcer. The pylorus and duodenum appear normal."
MALE, AGED 44 ON ENTRY	"Negative apart from small short oesophagus-type hiatus hernia."

Withdrawals

FEMALE, AGED 52 ON ENTRY	"Oesophagus and stomach outlined normally. A small incisura was seen just above the left fornix of the duodenal cap which, though a duodenal ulcer was not seen, is suggestive of duodenal ulceration."

DISCUSSION

DR. M. THOMPSON (*Newcastle*) asked if there was a moral obligation to put all patients with active rheumatoid arthritis on a dose of about 10 mg. prednisolone daily, and why this trial had shown such a different result from that of the original Cortisone/Aspirin trial.

PROF. KELLGREN replied that the different result was due to the fact that a different steroid had been used. In a previous trial conducted by the Joint Committee prednisolone had been shown to be significantly better than cortisone in rheumatoid arthritis, and it was not therefore surprising that a different result had been obtained in comparing prednisolone with aspirin or other analgesics.

He did not know the answer to the other question. The rising D.A.T. titre worried him. He felt, with the others, that the rheumatoid serum factor was a nasty thing to have in one's blood, but a longer follow-up was needed.

PROF. S. J. HARTFALL (*Leeds*) asked if one treated the titre or the patient.

PROF. KELLGREN replied by citing syphilis and the Wassermann reaction. One did not really know the significance of the Wassermann reaction, but if it became more strongly positive in a patient under treatment for syphilis it would be worrying, although the patient might be feeling fine.

PROF. HARTFALL did not consider the analogy a good one, since the significance of the rheumatoid factor in this mysterious disease was not known.

PROF. KELLGREN felt that there was increasing evidence that a high agglutinating titre in arthritis indicated a poor prognosis and a negative test a good one.

PROF. BYWATERS (*Taplow*) remarked that remission or progression could occur in individual patients irrespective of the D.A.T. All one could do was to observe the patient and the D.A.T. It was not yet possible to foresee prognosis from changes in the D.A.T. in serial measurements.

DR. F. DUDLEY HART (*London*) asked whether complete remission had been seen in either group of patients.

PROF. KELLGREN replied that one patient on prednisolone and one on aspirin had gone into complete remission before the end of the first year; they had had negative tests and *x* rays before entry. Both had defaulted from the trial. In reply to a question whether the D.A.T. had fluctuated, he said that the D.A.T. had been done at 3- and 6-monthly intervals, and that a few negative had become positive and *vice versa*.

DR. M. THOMPSON (*Newcastle*) said that the single adverse finding, in the prednisolone-treated patients, of significantly more positive D.A.T. results at the end of treatment, could be very important. The significance of the D.A.T. titre in the series investigated by Dr. Duthie and himself had been emphasized, and he felt it necessary that in these trials a standard uniform test should be carried out in each centre.

DR. J. GLYN (*London*) asked whether anything could be learned from the failures, *i.e.* from the patients who had been changed from one drug to another.

PROF. KELLGREN replied that, broadly speaking, the patients who had changed over had not done so well.

DR. H. F. WEST (*Sheffield*) thought that Dr. Thompson's first question on the moral obligation to give prednisolone should be answered more fully. They had been heavily involved in these therapeutic trials, but their present view was no different from that held at the beginning—namely that steroid therapy should be used for the severely affected, ill patients (*i.e.* about one in twenty).

DR. J. J. R. DUTHIE (*Edinburgh*) thought that, if the progress of erosions could be arrested, it was surely better to use prednisolone in early mild cases rather than in late severe ones.

DR. J. NORRIE SWANSON (*Toronto*) said that treatment should be suited to individual needs. A good regime was to try aspirin, and (if that failed) phenylbutazone, and (if that failed) G 27202, and (if that failed) steroids. A large-scale therapeutic trial could not dictate the best treatment for each individual patient.

PROF. KELLGREN replied that all the hazards of long-term steroid treatment including pharmacological adrenalectomy had not come out in the trial, but would become apparent in a few year's time. The complete answer was not yet available, but would require a trial and follow-up lasting 10 years. The results of the present trial did, however, give some general guidance to help decide the treatment of choice for individual patients.

Comparaison de la prednisolone à l'aspirine ou aux autres analgésiques dans le traitement de l'arthrite rhumatismale

RÉSUMÉ

(1) Dans un essai thérapeutique contrôlé, la prednisolone fut comparée à l'aspirine et aux autres analgésiques dans le traitement de l'arthrite rhumatismale.

(2) Huit centres participèrent à cet essai et 84 malades s'y soumirent au début. Quelques malades se désistèrent, moururent ou furent retirés, de façon qu'au bout de deux ans de traitement les résultats à dépouiller ne se basent que sur 77 cas; 41 d'entre eux allotés à la prednisolone et 36 aux autres analgésiques.

(3) Les malades traités par la prednisolone accusèrent une amélioration précoce et appréciable, confirmée par des indices cliniques et de laboratoire de la polyarthrite inflammatoire. Cette amélioration, bien que moins prononcée, fut encore significative au bout de deux ans.

(4) Dans le groupe des malades traités par des analgésiques, la fréquence des signes radiologiques de maladie articulaire érosive des mains et des pieds augmenta appréciablement au bout de deux ans, tandis qu'il n'y eut pas d'altérations appréciables dans le groupe traité par la prednisolone.

(5) Chez beaucoup de malades traités par la prednisolone, le titre d'agglutination des globules de mouton augmenta au cours des 2 ans de traitement, tandis qu'une telle augmentation ne se produisit que chez quelques malades traités par des analgésiques.

(6) Deux malades traités par des analgésiques moururent d'insuffisance cardiaque. Cinq malades traités par la prednisolone accusèrent des complications majeures (deux cas de psychose et trois d'ulcération peptique). Toutes ces complications majeures survinrent chez des malades recevant 20 mg. ou plus de prednisolone par jour. Chez des malades à la prednisolone il y eut aussi une augmentation du poids du corps, une élévation légère de la tension artérielle et une tendance au boursouflement (*mooning*) du visage. Pendant l'essai, la dose moyenne par jour de prednisolone fut progressivement réduite de 17,4 à 10 mg. et plus de la moitié des malades à la prednisolone reçut aussi de l'aspirine et d'autres analgésiques. On en conclut, que la dose optimum par jour pour un traitement à longue échéance dans un cas moyen d'arthrite rhumatismale ne doit pas dépasser 10 mg. de prednisolone.

Comparación de la prednisolona a la aspirina o a otros analgésicos en el tratamiento de la artritis reumatoide

SUMARIO

(1) En una investigación terapéutica controlada se comparó la prednisolona a la aspirina y a otros analgésicos en el tratamiento de la artritis reumatoide.

(2) Ocho centros participaron en esta investigación, empezando con un total de 84 enfermos. Algunos de estos desistieron, murieron o fueron retirados, de manera que al cabo de dos años quedaron 77 casos para analizar; 41 de ellos tratados con prednisolona y 36 con otros analgésicos.

(3) Los enfermos tratados con prednisolona acusaron precozmente una mejoría apreciable, confirmada por los índices clínicos y de laboratorio, empleados en la poliartritis inflamatoria. Esta mejoría, aunque menos pronunciada, aún fué significativa al cabo de dos años.

(4) En el grupo de enfermos tratados con analgésicos, la frecuencia de signos radiológicos de enfermedad articular erosiva de las manos y de los pies aumentó significativamente al cabo de dos años, mientras que no se vieron alteraciones apreciables en el grupo tratado con la prednisolona.

(5) En muchos enfermos tratados con prednisolona, el título de aglutinación de globulos de oveja aumentó durante los dos años de tratamiento, mientras que tal aumentación se produjo sólo en algunos enfermos tratados con analgésicos.

(6) Dos enfermos tratados con analgésicos murieron de insuficiencia cardiaca. Cino enfermos tratados con prednisolona acusaron complicaciones mayores (dos casos de sicopatía y tres de ulceración péptica). Todas estas complicaciones mayores ocurrieron en enfermos recibiendo 20 mg. o más de prednisolona diaria. Los enfermos tratados con prednisolona presentaron también un aumento del peso corporal, un ascenso ligero de la tensión arterial y una tendecia a la "cara de luna". Durante la investigación, la dosis diaria media de prednisolona fué progresivamente reducida de 17,4 mg. a 10 mg. y más de la mitad de los enfermos tratados con prednisolona recibían además aspirina y otros analgésicos. Se concluye que la dosis diaria óptima en el tratamiento de plazo largo en un caso ordinario de artritis reumatoide no debe rebasar 10 mg. de prednisolona.

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A METHOD FOR TESTING ANALGESICS IN RHEUMATOID ARTHRITIS USING A SEQUENTIAL PROCEDURE

BY

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In the management of patients with inflammatory erosive arthritis of the rheumatoid type, general measures such as rest in bed and splintage followed by graded exercises form the basis of treatment during periods of disease activity. Medication with drugs is of value in relieving the painful symptoms of the arthritis, but there is no agreement as to which of the presently available drugs should be used and new preparations are continually being introduced. The object of this investigation was to devise a method whereby the effectiveness of drugs in controlling symptoms in patients admitted to hospital for treatment of arthritis by general measures could be rapidly assessed. It was hoped to reduce to a minimum the number of patients required for the study by the use of sequential analysis. Trials of this kind should cause the patient no hardship and should involve the minimum disturbance of ward routine and little additional labour for nursing and medical staff.

Methods

Duration.—In some preliminary studies, aspirin, a new analgesic, and placebo tablets were given for periods of 3 or 6 days with daily assessments; but it soon became clear that a longer period of therapy, fewer assessments, and the elimination of a placebo period were needed to fulfil the requirements mentioned above. The final design consisted of a 2 weeks' trial for each patient, during which each of the two drugs being compared was given for a period of one week, assessments being made on the second, fifth, and seventh day of each week of medication. In many patients such 2-week courses were repeated during the whole of their stay in hospital.* The trials were all of the double-blind type; assessments being made at approximately the same time each morning by the medical resident and the technicians attached to the unit during the course of their routine duties in the ward.

* Toxic reactions observed after the initial fortnight are included in the section on drug toxicity. All other data relate only to the first 2 weeks.

Criteria of Assessment

(1) The severity of pain and stiffness, reported by the patient to the resident, each characteristic being rated by the resident on a numerical scale.

(2) The strength of grip (in mm. Hg), measured by squeezing a bag attached to a sphygmomanometer and inflated to a pressure of 20 mm. Hg, the value of three grips with each hand alternately being recorded. The figures accepted were the highest that the patient could maintain for a period of 2 to 3 seconds. The grip tests were recorded by the technical staff.

In addition, other tests (such as finger swelling measured by ring size, the time taken to tie knots, and the degree of tenderness elicited by squeezing affected joints) were used at some stage, but these proved less useful. Only the records of pain, stiffness, and strength of grip were used throughout the trials, and only these characteristics have been subjected to analysis.

Patients.—The trials were conducted in the wards of the Manchester Royal Infirmary and the Devonshire Hospital, Buxton, and all patients with active inflammatory polyarthritis of the rheumatoid type admitted to the University Centre's beds during the trial period participated unless there were special contraindications to their inclusion. There were four main reasons for such exclusion:

(*a*) No involvement of the hands or such deformity of the hands as to make the grip test inapplicable.
(*b*) Corticosteroid therapy immediately before admission.
(*c*) A history of previous toxic reactions to the drugs being investigated.
(*d*) Complicating diseases that might be aggravated by the drugs being investigated.

The patients were not told that a comparison of drugs was being made, but they were told that the object of the procedures was to determine which tablet suited them best as individuals, and this was in fact a subsidiary but important object of the trial procedure.

Drugs.—In the trials so far conducted, calcium aspirin in a daily dose of 5 g. was used as the standard medication, since this represented the routine medication used

in our wards before the trial programme, and this has been compared with four other forms of medication:

(1) A new aspirin-like agent, 4-hydroxy-isophthalic acid (HIPA), given in a dose of 6·7 g. daily.

(2) Prednisone in a dose of 30 mg. daily.

(3) Phenylbutazone in a dose of 300 mg. daily.

(4) N-acetyl-p-aminophenol (NAPAP) marketed as "Panadol" in a dose of 7·5 g. daily.

In each trial alternate patients in order of admission were given aspirin during the first week and the other drug during the second week, the order of treatment being reversed in the other patients. When the dosage of the two drugs was similar they were made up in tablets that looked alike and they were given in five daily doses. When the dosage differed as with prednisone and phenylbutazone the patients received two lots of tablets, large and small, during each week, so that when comparing prednisone with aspirin one week's therapy consisted of prednisone plus dummy aspirin, while during the other week it was aspirin plus dummy prednisone.

Sequential Analysis

The length of three of the four trials reported was determined by sequential analysis. Traditional significance tests are valid only if the number of cases included in the sample is determined independently of the observations. In practice, no doubt, research workers have often gone on collecting data until a "significant" result was obtained. This procedure leads to erroneous conclusions unless special "sequential" statistical techniques are employed. Such techniques were first developed during World War II for industrial application. Their use in clinical trials has been widely discussed (for example, by Armitage (1954) and Bross (1958)) and they have been employed in a few trials listed by Bross (1958). In therapeutic trials, the idea of subjecting data to continuous analysis as they become available has special attractions, since it is often very desirable that a trial be discontinued as soon as it can clearly be established that one treatment is more effective than another.

The particular sequential technique employed in the present trials is the sequential *t*-test. We shall proceed to describe in non-technical language the main problems which arose in the application of this technique, and also to show the actual calculations, which are quite simple. Additional information may be found in the Appendix.

The essence of a sequential trial of two treatments is to perform a quick analysis, as each additional set of data comes in, to determine whether (*i*) enough data have accumulated for a decision, or (*ii*) more data need to be collected. Alternative (*i*) in the present instance could come about in two ways: we may stop because the data so far collected indicate with reasonable certainty either that there is no difference between drugs or that there is an appreciable difference.

To select a particular procedure, we must determine what we mean by "with reasonable certainty" and fix a target difference which we agree to regard as "appreciable". For the present trials "with reasonable certainty" was taken to mean that the chance of a correct decision should be nineteen out of twenty. For a sequential *t*-test, the target difference is fixed in terms of the variability between observations for different patients. This form of statement is not in itself very informative. The variability is measured by the standard deviation and will depend on the index chosen to assess the effect of the drugs. In the present instance the target difference corresponded to 0·6 of the standard deviation of the observations for individual patients. The results suggest that this target is smaller than the difference between aspirin and a placebo or between prednisone and aspirin. A trial conducted in accordance with the method chosen should, therefore, detect any substance which is as much superior to aspirin as aspirin is to a placebo; it should also detect any medication which is not much better than an inert substance.

For the sequential procedure it was necessary to select a single index to measure the difference between the drugs. The main aim of statistical analysis is to disentangle, as far as possible, the differences due to the drugs from those due to other fluctuations in the observations (due to "natural" variations in the activity of the disease, changes in the patient's mood, etc.). It was found in the preliminary experiments that differences between drugs seemed largest in relation to other fluctuations when measured by grip strength. Hence the grip strength was used as the index for the sequential test.

When a new analgesic drug is to be tested, the only information usually available relates to its toxicity and apparent analgesic properties in animals and human volunteers. Its rate of action and whether, in the case of effective drugs, its withdrawal may be followed by a "rebound" of symptoms is not known. These considerations might suggest that in the present scheme only the last assessment on each drug (*i.e.* when the patient has been taking the medication for 7 days) should be taken into account. However, since these and other factors may be of varying importance with different drugs, it seemed best to use the simplest method and to give equal weight to all assessments, *i.e.* to compare the means of the readings of the features assessed

while the patient was receiving one drug with those recorded while he was receiving the other drug.

Table I shows how the grip records of two patients (the first two in the prednisone/aspirin trial) were handled. The two patients were given the drugs in different order. For each patient the mean grip strength was first computed for each week. The difference between the two means was then taken, the mean for the prednisone week being always subtracted from the mean of the aspirin week (whichever week came first). The differences so obtained, which will be called mean grip differences,* are shown in the last line of the Table.

One further step was involved in preparing the data for the sequential analysis. It was found that, as a rule, the patient's condition tended to improve considerably as the trial proceeded independently of drug action. Consequently, if two equally effective or ineffective drugs are compared, the one given in the second week would usually appear to be appreciably better. This phenomenon is further described below. To take account of it in the sequential analysis, the mean grip differences were added together for pairs of successive patients; the two members of each pair differed in the order in which they had received the drugs.

The procedure is illustrated in Table II, which relates to the prednisone/aspirin trial. For successive patients who received prednisone in the first week and completed the trial, we denote the mean grip differences by x_1, x_2, x_3 . . .; for patients who started on aspirin and completed the trial we denote the mean grip differences by y_1, y_2, y_3 . . . Thus, as the observations become available,* we compute

* Both the sequential analysis and all other analyses of grip data in this paper (apart from Table X) make use only of the mean grip differences for each patient. Only in Table X are successive assessments shown separately. Figures for pain and stiffness depend only on mean differences computed in the same way.

* As patients entered the trial they were alternately assigned to start on prednisone or aspirin. If they had all completed the trial, the observations would have come in in the order x_1, y_1, x_2, y_2, x_3, y_3 . . . However, some patients were withdrawn because of suspected toxicity, faulty diagnosis, etc., and it happened, therefore, that two complete records suitable for sequential analysis became available for prednisone-starters, with no intermediate aspirin starter.

TABLE I

SPECIMEN ANALYSIS OF GRIP RECORDS

Serial No. of Assessment	Patient A		Patient B	
	Medication	Grip Strength (mm. Hg)	Medication	Grip Strength (mm. Hg)
1	Prednisone	190	Aspirin	105
2		183		88
3		195		97
4	Aspirin	212	Prednisone	105
5		200		133
6		187		143
Mean of First Week	Prednisone	189·3	Aspirin	96·6
Mean of Second Week	Aspirin	199·7	Prednisone	127·0
Mean Difference between Weeks	Aspirin minus Prednisone	+10·4	Aspirin minus Prednisone	−30·4

Note: The grip strength at each assessment is itself the mean of six readings, three being taken on each hand.

TABLE II

SEQUENTIAL ANALYSIS OF PREDNISONE TRIAL

Serial No. of Pair of Patients	Mean Grip Differences*		Sum of Differences for Successive Pairs	Cumulative Total of Previous Column	Squared Sums	Cumulative Total of Previous Column	Sequential Criterion
	Prednisone-starters	Aspirin-starters					
i	x_i	y_i	$d_i = x_i + y_i$	Σd_i	d_i^2	Σd_i^2	$z_i = \frac{(\Sigma d_i)^2}{\Sigma d_i^2}$
1	+10	−30	−20	−20	400	400	1·00
2	+2	−56	−54	−74	2,916	3,316	1·65
3	0	−30	−30	−104	900	4,216	2·57
4	−7	−39	−46	−150	2,116	6,332	3·55
5	+16	−60	−44	−194	1,936	8,268	4·55
6	+18	−51	−33	−227	1,089	9,357	5·51
7	+46	−78	−32	−259	1,024	10,381	6·46

* The mean grip strength for the prednisone week has been substracted from the mean for the aspirin week.

successively x_1+y_1, x_2+y_2, x_3+y_3, . . . The sums so obtained will be denoted by d_1, d_2, d_3, . . .
In particular, from Table I, we have for the first pair

$$10{\cdot}4 + (-30{\cdot}4) = -20{\cdot}0$$

(The figures in Table II have been rounded for convenience.)

The remaining computations for the sequential analysis are also given in Table II. The sequential criterion computed at each stage (denoted by z_i) is given by the formula

$$z_i = \frac{(\Sigma\ d_i)^2}{\Sigma\ d_i^2}$$

Here $\Sigma\ d_i$ denotes the total of all the ds so far available, and $\Sigma\ d_i^2$ denotes the total of the squares of all the ds so far available.

The sequential criterion z thus computed is compared with two predetermined numbers, an upper and a lower stopping limit. If the value of z_i exceeds the upper limit, the trial ends because the data are sufficient to indicate that there is an appreciable difference between the drugs. If z_i falls short of the lower limit, the trial is ended because the data are sufficient to show that there is no appreciable difference between the drugs. So long as z remains between the upper and the lower limits, additional observations are taken.

Stopping limits for the present trials are shown in Table III up to the 30th pair of patients. The limits change as the number of observations increases. By referring back to Table II, it may be seen that in the prednisone/aspirin trial the sequential criterion stood at 5·51 after the sixth pair,* which is below the upper stopping limit at this point (5·58). After the sixth pair, however, the sequential criterion jumped to 6·46 and thus exceeded the upper stopping limit for the seventh pair (5·50). In addition to the stopping limits, Table III shows the course of the sequential analysis of the phenylbutazone/aspirin and NAPAP/aspirin trials.

The position of the stopping limits is such that the trials have the characteristics specified above, *i.e.* essentially a 1 in 20 chance of a wrong decision. As is explained in the Appendix, lists of stopping limits are readily available for trials for which it is desired to specify other characteristics.

* It will be noted that it is not possible to cross the stopping limits before the sixth pair. It is not, therefore, essential to compute z_i itself until this point is reached, except to see how the trial is going. It is also possible to simplify the arithmetic in other ways.

TABLE III

SEQUENTIAL DATA FOR TWO TRIALS AND STOPPING LIMITS

Serial No. of Pair of Patients	Phenylbutazone Trial		NAPAP Trial		Stopping Limits	
	Sums of Mean Grip Differences d_i	Sequential Criterion z	Sums of Mean Grip Differences d_i	Sequential Criterion z_i	Lower	Upper
1	−3	1·00	−27	1·00	—	—
2	0	1·00	+43	0·10	—	—
3	+21	0·75	−8	0·02	—	—
4	−10	0·13	−9	0·0003	—	—
5	−23	0·18	+17	0·09	—	—
6	−14	0·48	+4	0·13	—	5·58
7	+11	0·21	+2	0·16	—	5·50
8	−18	0·74	+2	0·19	—	5·50
9	+4	0·58	+23	0·61	0·11	5·51
10	−31	1·46	+11	0·90	0·23	5·56
11	−17	2·12	+32	1·71	0·35	5·61
12	+29	0·69	+23	2·41	0·48	5·69
13	+3	0·60	+6	2·67	0·61	5·77
14			+5	2·89	0·74	5·87
15			−17	2·06	0·87	5·97
16			+6	2·29	1·00	6·08
17			0	2·29	1·14	6·19
18			+8	2·59	1·28	6·31
19			+23	3·35	1·42	6·43
20			+4	3·52	1·56	6·55
21			+35	4·49	1·71	6·68
22			+36	5·48	1·85	6·81
23			−2	5·36	2·00	6·94
24			+10	5·79	2·14	7·07
25			+33	6·76	2·29	7·20
26			+6	7·05	2·43	7·34
27			−8	6·59	2·58	7·47
28			+21	7·39	2·73	7·61
29			+20	8·17	2·88	7·75
30					3·03	7·89

Note: Values of d_i have been rounded, so that the z_i calculated from them would not necessarily be in precise agreement with those given.

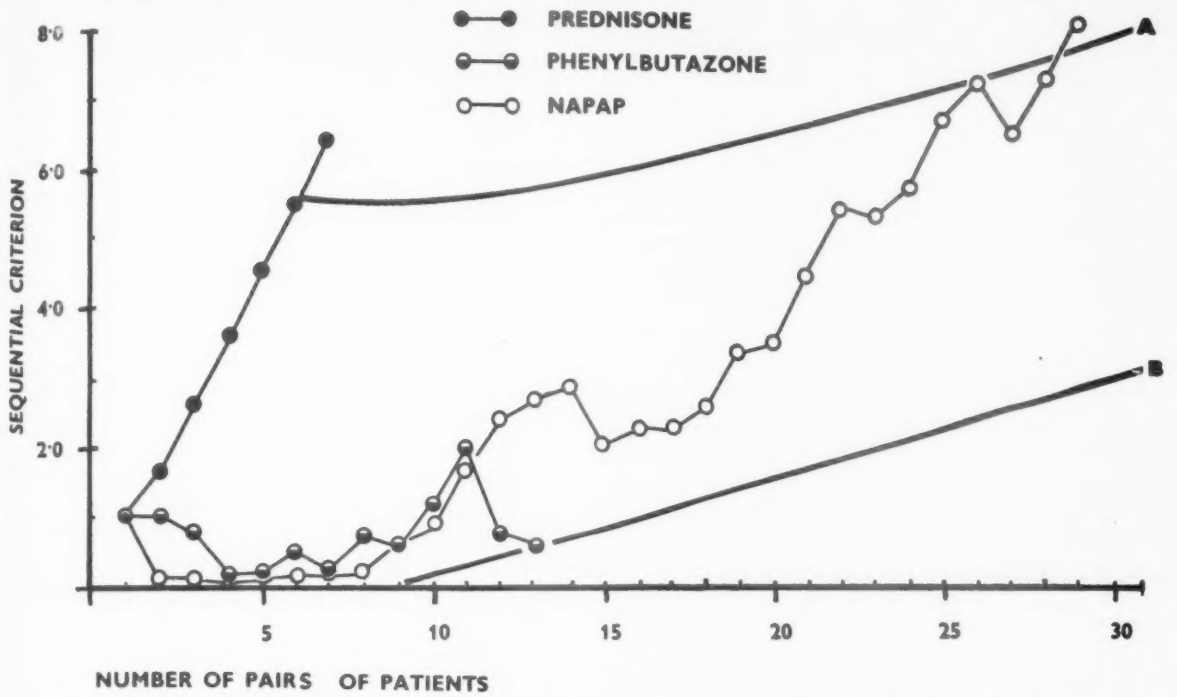

FIGURE.—Boundaries for "Difference" and "No Difference" between drugs for the sequential test employed, and sample paths of the prednisone phenylbutazone, and NAPAP trials.
(A) Drug better or worse than Aspirin
(B) No difference between the Drug and Aspirin

It is informative to follow the progress of a sequential trial on a chart such as that shown in the Figure. The stopping limits are represented by two heavy black lines. Successive values of the sequential criterion z_i can be entered as the trial proceeds. The trial continues so long as z_i remains between the heavy black lines. The crossing of one of the lines is the signal for ending the trial. In the Figure, the course of all the three sequential trials reported in the present paper is shown in this way.

Table IV summarizes the sequential trials in regard to duration and outcome. The number of patients required till a decision was reached varied widely. This is in part a matter of chance. However, the difference in effectiveness between the medications being tested is an important determinant. If the difference between them is as great as the "target" difference which the procedure selected is designed to detect, the average number of pairs required is likely to be about fifteen. If the difference exceeds the "target" then the trial usually ends earlier, as was the case in the prednisone trial, because such a large difference can be quickly detected. (No doubt the prednisone trial happened to be a particularly short one even for a comparison

TABLE IV
DURATION AND RESULTS OF SEQUENTIAL TRIALS

Drug*	Dose (per day)	No. of Pairs Required	No. of Patients Withdrawn before Decision Reached†	Result
Prednisone	30 mg.	7	0	Superior to aspirin
Phenylbutazone	300 mg.	13	5	Similar to aspirin
NAPAP	7·5 g.	29	4	Inferior to aspirin

* Each drug was compared with 5 g. calcium aspirin per day.
† Only patients withdrawn because of possible toxic effects of the medication are counted here. Withdrawals for other reasons (*e.g.* faulty initial diagnosis) are not included (see text).

where the true difference is considerable.) In the case of phenylbutazone there was almost no difference between the drugs. Such a trial usually takes somewhat longer than one where the difference is at the "target" level. The longest runs, however, will usually occur when the difference between the drugs is about half as big as the "target" difference. The NAPAP trial was probably long partly because the difference between NAPAP and aspirin as measured by grip was small, but not negligible.

Analysis by Traditional Procedures

Numbers of Patients.—The sequential analysis was used only to determine when sufficient patients had been included in the trials. After each trial had been terminated, a full analysis of the results was made by traditional statistical methods. The results of this analysis are summarized in Tables V to X (below).

These Tables include a considerably larger number of patients than that used for the sequential procedure. There are two main reasons for this. First, observations were recorded for all patients, but initially only those with an erythrocyte sedimentation rate of over 30 mm./hr (Westergren) and without radiological changes in the hands were used in the sequential analysis. (The first restriction was later abandoned, and the second considerably relaxed.) Secondly, some patients were included intentionally in all trials in excess of those required for decision by the sequential procedure, because patients who had already started the trial when the sequential analysis indicated that an answer had been obtained completed their courses. Moreover, since it was not always possible to switch immediately to the testing of a new drug, the old trial was in two instances continued for some additional weeks.

The additional cases are especially helpful, because it is not strictly correct to analyse data collected in a sequential trial by traditional statistical procedures. The risk of error on the ground is, however, greatly diminished by the additional cases; standard errors may, therefore, be interpreted fairly confidently as though the length of the trials had been fixed without looking at the data as they accumulated.

Although the patients for whom complete records were obtained exceed those used in the sequential analysis, the total numbers admitted to the trials were greater still. Apart from those who had to be withdrawn from the trials because of the toxic effects of the drugs, there were patients whose treatment was altered or who were transferred to another hospital during the trial period for reasons unconnected with the trials or in whom the original diagnosis was shown to be incorrect after they had started on the trial. There were also a few in whom the assessments were not all made, or were improperly entered, etc. In all, 35 patients were admitted to the prednisone trial, 48 to the phenylbutazone trial, and 100 to the NAPAP trial.

Tables VI, IX, and X (as also the Appendix Tables) present, in addition to the three trials which were analysed sequentially, data from the HIPA/aspirin trial. HIPA was used in preliminary trials in which various schemes (differing in length of administration of drugs, frequency of assessments, etc.) were tried. In all, 27 patients were involved and thirteen patients participated in the final series of these preliminary trials in which the procedure was identical with the subsequent trials (*i.e.* one week on each of two drugs, three assessments per week), but sequential analysis was not yet employed. The results for these thirteen patients are reported below. As explained in the Appendix, this experience provided material helpful in the choice of appropriate sequential methods.

Comparison of Medications.—The results of the NAPAP trial are summarized in Table V. In reading this Table it should be remembered that an improvement in the patient's condition is reflected in an *increase* of the score for grip, but in a *decrease* of the scores for pain and stiffness. Hence the superiority of aspirin is indicated by positive figures for grip, and negative figures for pain and stiffness.

TABLE V

DIFFERENCE IN MEAN DAILY ASSESSMENTS BETWEEN NAPAP AND ASPIRIN
(ASPIRIN RATINGS MINUS NAPAP RATINGS)

Assessment	(*a*) Patients who Started on NAPAP	(*b*) Patients who Started on Aspirin	Mean of (*a*) and (*b*)
Grip (mm. Hg) ..	+11	0	+5·5
Pain*	−0·29	−0·06	−0·175
Stiffness*	−0·25	+0·08	−0·085
No. of Patients† ..	38	37	

* Pain and stiffness were assessed in a rating of patients' statements on an arbitrary scale running from 0 (no pain or stiffness) to 3 (very severe pain or stiffness).

† Numbers of patients are those for pain and stiffness. Grip records were somewhat less complete and the figures were based on 34 and 35 patients respectively (for the two order groups).

The order in which the drugs are given makes an appreciable difference, as explained earlier, since the assessments tend to improve between the first and second weeks independently of medication. If the results for the patients who first received aspirin and those who first received NAPAP are averaged, the

effect of the "spontaneous improvement" may be assumed to cancel out. The figures given in the last column of Table V are therefore estimates of the difference in effect between aspirin and NAPAP.

Figures derived in the same way as the last column of Table V (correct to two places of decimals) are shown for all four trials in Table VI (overleaf). The method of calculation of the standard errors is detailed in Section 2 of the Appendix. The directions of the differences correspond, of course, to the conclusions listed in Table IV.

The observations on grip, pain, and stiffness were consistent; *i.e.* improved grip was usually accompanied by decreased pain and stiffness. The differences were greatest between aspirin and HIPA but, owing to the small numbers in this trial, the standard errors were large. In the preliminary observations mentioned earlier, which included the administration of a placebo, the results suggested that there was little difference between HIPA and the placebo.

The differences between aspirin and prednisone were also large, but the superiority of aspirin over NAPAP was less clearly marked, especially as measured by grip. None of the differences observed between aspirin and phenylbutazone were significant.

Drug Toxicity.—The numbers of patients developing manifestations which could be attributed to toxic effects of the drugs are indicated in Table VII (overleaf), and further details are given in Table VIII (overleaf).

In these trials any symptoms or signs which might represent side-effects of the treatment were recorded as toxic effects of the medication being given at the time. The recorded incidence of toxic effects is probably therefore unduly high, since some of these manifestations may have been unrelated to the medication. Such errors would, however, be likely to occur with about equal frequency with aspirin and with the drug being compared.

There was no significant difference ($p > 0{\cdot}5$) between the proportions of patients in whom toxic effects were ascribed to aspirin in the three trials, namely 23 per cent. (7/31) in the prednisone trial, 22 per cent. (10/45) in the phenylbutazone trial, and 15 per cent. (14/94) in the NAPAP trial, and this suggests that such effects were recorded consistently in each trial. A satisfactory comparison of the proportions of those who continued to take the different medications in alternate weeks who developed toxicity after the first fortnight is not possible, since the factors determining whether patients continued with this programme varied from trial to trial and sometimes during the course of a single trial.

Aspirin.—In the 170 patients who received aspirin, toxic effects were ascribed to the drug in 48 (28 per cent.). Five were withdrawn from a trial during the first course and five during later courses, and three others completed one or more 2-week courses, but were not given further courses on account of these effects, a total of thirteen (8 per cent.).

28 (17 per cent.) suffered from either deafness, tinnitus, or both; four were withdrawn during a trial course, and another was not given a third course on account of these symptoms. A further patient complained of dizziness.

Gastro-intestinal disturbances, usually anorexia and nausea, but occasionally epigastric pain, vomiting, or diarrhoea, were noted in twenty patients (12 per cent.) necessitating withdrawal during a trial course in four and at a later stage in two others who continued on the trial regime after the first fortnight.

Mild skin rashes occurred in three patients receiving aspirin and all were withdrawn from the trials. One occurred at the end of the first week of the trial; it cleared rapidly when the aspirin was discontinued but recurred some weeks later when aspirin was resumed in lower dosage. In the others the rashes occurred during the 4th and 8th weeks respectively. In each case the rash cleared up rapidly and its relationship to the medication appeared doubtful; in one of them patch tests with aspirin and NAPAP were negative and the other received aspirin subsequently without adverse effects.

One patient complained of headache and nausea and another of headache and "fullness of the face" while taking aspirin during the second fortnight; one was withdrawn during and the other after the completion of the second fortnight.

One patient complained of depression on aspirin, but this may have represented a withdrawal effect of prednisone, which she had received in the previous week.

One patient had spontaneous epistaxis while on aspirin which had also occurred during her previous week on NAPAP; the plasma prothrombin concentration was found to be 50 per cent. and there was other evidence of liver damage. The trial regime was not continued, but subsequently she tolerated aspirin in lower dosage without ill-effects.

Prednisone.—Only one of the thirty patients receiving prednisone developed toxic effects necessitating withdrawal from the trial; she suffered from essential hypertension and when on prednisone in

TABLE VI

DIFFERENCES IN MEAN DAILY ASSESSMENTS BETWEEN EFFECT OF ASPIRIN AND OTHER DRUGS TESTED

(RATINGS FOR DRUGS SPECIFIED SUBTRACTED FROM THOSE FOR ASPIRIN)

Assessment	Drug Compared			
	HIPA	Prednisone	Phenylbutazone	NAPAP
Grip (mm. Hg)	+25±5·1	−15±4·0	+1±2·5	+6±1·6
Pain (Arbitrary Rating)	−0·33±0·22	+0·21±0·07	+0·03±0·07	−0·18±0·06
Stiffness (Arbitrary Rating)	−0·42±0·11	+0·12±0·09	+0·03±0·07	−0·09±0·05
No. of Patients	13	29	37	75

Notes: Numbers of patients are those for pain and stiffness. The numbers included who were first given one or the other drug differed at most by 1. Grip records were slightly less complete. The numbers of patients tested for grip may be seen in Table X.
For Grip Strength, a positive sign indicates that aspirin gave a superior result, and a negative sign indicates that the drug tested gave a superior result.
For Pain and Stiffness the opposite is the case.

TABLE VII

INCIDENCE OF DRUG TOXICITY

Daily Dosage of Drug compared with Calcium Aspirin 5 g. Daily	Number of Patients					Average Number of Days		Toxicity (Number of Patients)								
								In First Course					In Any Course			
								Total			Withdrawn from Trial		Total			Wit fro
	Starting First Course	Satisfactory Data re Toxicity*	Starting Further Course(s)	Receiving Drug Specified	Receiving Aspirin	On Drug Specified	On Aspirin	On Drug Specified Only	On Aspirin Only	On Both	On Drug Specified	On Aspirin	On Drug Specified Only	On Aspirin Only	On Both	On Drug Specified
Prednisone 30 mg. ..	35	31	7	30	31	8·7	8·5	2	7	1	1	1	2	8	1	1
Phenylbutazone 300 mg.	48	47	21	44	45	13·1	13·1	3	10	0	2	3	3	19	0	2
NAPAP 7·5 g.	100	98	68	97	94	12·8	13·1	12	9	5	4	1	14	13	7	6

* One patient was excluded because the diagnosis of rheumatoid arthritis was found to be incorrect shortly after her entry into the trial, and the others because the forms on which toxicity was recorded were lost.
† In two further patients in the phenylbutazone trial and one in the NAPAP trial the trial courses were completed, but further courses were not given owing to toxic effects of calcium aspirin.

TABLE VIII

TOXIC EFFECTS

Trial	No. of Patients Experiencing Toxicity		Symptoms and Signs of Toxicity									
	Total	Causing Withdrawal from Trial	Deafness, Tinnitus, or Both	Dizziness	Gastrointestinal Symptoms	Cutaneous Lesions	Buccal Ulceration	Hypertension	Headache	Depression	Epistaxis	Not Stated
Prednisone	3	1	2					1 (1)				
Aspirin	9	1	4		6 (1)					1		
Phenylbutazone	3	2			1	1 (1)	1 (1)					
Aspirin	19	8	11 (2)		7 (2)	2 (2)			1 (1)			1 (1)
NAPAP	21	6	2	1	18 (6)						1	
Aspirin	20	4	13 (2)	1	7 (1)	1 (1)			1		1	

Note: Figures in brackets indicate the numbers of patients withdrawn from the trial or in whom the trials were discontinued because of the toxic manifestations indicated.

the second week of the trial her blood pressure rose abruptly and the prednisone was discontinued. The blood pressure then fell rapidly to its previous level.

One patient complained of slight tinnitus and another of slight deafness in one ear, in each case at the end of the first week of the trial when they had received prednisone. Symptoms continued in the latter throughout the week on aspirin but rapidly subsided after she changed back to prednisone for a further week. In the other the tinnitus subsided after 2 days on aspirin. In view of the precautions that were taken to ensure that the patients received the correct drug (each dose of tablets for a patient being indicated on a chart which was initialled by the nurse giving it), it is unlikely that these two patients had received aspirin in error, but also unlikely that these symptoms were attributable to the prednisone. Wolf and Pinsky (1954) have called attention to the unexpected symptoms and occasionally signs which may follow administration of even an inert placebo.

Phenylbutazone.—Toxic effects were recorded in only three (7 per cent.) of the 44 patients who received it. In this trial, in view of the potentially serious side-effects of phenylbutazone, seven patients who gave a history of adverse reactions when phenylbutazone had been given previously and ten others who had conditions predisposing them to serious side-effects were excluded from the trial. The latter included five with known or suspected peptic ulcers, two with severe hypertension, two with auricular fibrillation, and one with a refractory anaemia. But for this selection the incidence of toxic effects observed with phenylbutazone would almost certainly have been higher. Thus one patient, who was included in the trial despite a history of having developed soreness of the mouth when previously taking phenylbutazone, again developed ulcerative stomatitis after 5 days on phenylbutazone in his first course and had to be withdrawn from the trial.

One patient who suffered from chronic eczema of the hands complained of increased itching without objective change in the rash after 3 days on phenylbutazone and was also withdrawn.

The third patient who complained of transient nausea while receiving phenylbutazone was not withdrawn from the trial.

NAPAP.—Toxic effects were encountered in 21 (22 per cent.) of the 97 patients receiving NAPAP, seventeen of them in the first course; six (6 per cent.) were withdrawn from the trial on this account, four of them during the first course. Seven of these 21 patients also experienced toxic effects from aspirin.

Gastro-intestinal disturbances, similar to those encountered with aspirin occurred in eighteen patients, in sixteen of them in the first course. Four patients were withdrawn during the first course and two during later courses on this account. Two of the eighteen patients also had gastro-intestinal upsets from aspirin; five others in the trial had gastro-intestinal disturbances on aspirin but not on NAPAP. Gastro-intestinal disturbances on one drug only were significantly commoner with NAPAP ($p < 0{\cdot}03$).

One patient complained of short episodes of tinnitus and had an attack of vertigo and vomiting on NAPAP during the first course but completed a second course without trouble, and another who received NAPAP first noted mild deafness on this which became much worse with aspirin, regressed during the second week on NAPAP, and became so severe after changing back to aspirin that the trial regime was dicontinued 2 days later.

Thus, in the dosages employed the incidence of toxicity was much the same with NAPAP and aspirin.

"Spontaneous Improvement."—Several factors probably contribute to the spontaneous improvement with time which is usually observed after admission to hospital regardless of the medication. These may include the effect of rest in bed, increasing familiarity with hospital environment, and, in the case of grip, practice in the use of the apparatus. The natural history of rheumatoid arthritis is usually one of relapses and remissions; the tendency for patients to seek advice and to be admitted to hospital at the height of a relapse and therefore about to pass into some degree of spontaneous remission in the natural course of the disease may be important, but is probably less so in short-term trials of this type than in studies designed to assess the long-term effects of treatment on the disease.

Table IX (overleaf) shows estimates of spontaneous improvement. The method by which these are obtained is explained in the Appendix. Briefly, the figures in Table IX measure the improvement which went on between the first and second trial weeks, whatever the order in which the drugs were given. The figures represent the increases in mean grip and the decreases in the mean pain and stiffness ratings between the first and second weeks.

It will be seen that the spontaneous improvement is substantial in relation to the drug effects. In a clinical trial not designed to allow for it, an ineffective treatment could well be credited with substantial therapeutic value simply on account of the spontaneous improvement.

TABLE IX

ESTIMATES OF "SPONTANEOUS IMPROVEMENT"
CHANGE FROM FIRST TO SECOND WEEK IN MEAN DAILY ASSESSMENT

Assessment	Trial			
	HIPA	Prednisone	Phenylbutazone	NAPAP
Grip	+5±5·1	+20±4·0	+6±2·5	+6±1·6
Pain	−0·06±0·22	−0·28±0·07	−0·26±0·07	−0·11±0·06
Stiffness	−0·17±0·11	−0·33±0·09	−0·27±0·07	−0·16±0·05

In view of the size of the standard errors, all the estimates for spontaneous improvement from the four trials are in moderately good agreement, except that the spontaneous improvement in grip seems definitely larger for the prednisone trial than the other trials. On *a priori* grounds it would be expected that, even apart from variations due to the small number of patients, the estimates of spontaneous improvement would not be exactly the same with different pairs of drugs owing to such factors as withdrawal effects.

The unusually large spontaneous improvement in grip in the prednisone trial is puzzling. If it were particularly small, explanations would readily suggest themselves, for example, that a "rebound" of symptoms on withdrawal of prednisone had partially masked the effects of aspirin or that the prednisone had resulted in such complete remission of symptoms that the effects of spontaneous improvement were obscured.

It is possible to obtain a more detailed insight by following the successive assessments separately rather than merely the changes from the mean of one week to the mean of the next. For grip the situation may be seen in Table X.

In the prednisone trial it will be seen that the grip strength of those who started on prednisone fell upon changing to aspirin, but recovered to the final level of the previous week which was very much above the level at the beginning of the trial. Too much emphasis should not be placed on these changes between successive assessments: the numbers of patients in this trial were relatively small and the chance variation was difficult to analyse since successive changes in the same patient could not be assumed to be independent. Comparison with the other trials, however, suggested that the fall in grip strength on changing from prednisone to aspirin could not be due entirely to a "steroid withdrawal rebound" since a fall was also observed on changing from aspirin in each of the other trials and also on changing from phenylbutazone to aspirin.

Discussion

Pope's dictum that "the proper study of mankind is man" is peculiarly apposite to the study of the effectiveness of drugs in relieving pain arising from human disease. Pain is a complex personal experience and its intensity and effects are influenced by many factors both within and without the individual experiencing it (Hardy, Wolff, and Goodell, 1952; Beecher, 1956). The effects of drugs noted in experiments on animals and healthy human beings subjected to painful stimuli may thus have little bearing on their value in relieving pain in clinical

TABLE X

SEQUENCES OF ASSESSMENTS
MEAN GRIP STRENGTH (mm. Hg)

Trial		HIPA/Aspirin		Prednisone/Aspirin		Phenylbutazone/Aspirin		NAPAP/Aspirin	
Drug given First		HIPA	Aspirin	Prednisone	Aspirin	Phenyl-butazone	Aspirin	NAPAP	Aspirin
Assessment No.	1	**148**	**78**	130	**111**	106	**106**	98	79
	2	142	**91**	147	**116**	111	**118**	97	81
	3	144	**107**	158	**112**	117	**114**	97	89
	4	**180**	64	**141**	136	**113**	111	**108**	82
	5	**169**	70	**148**	150	**120**	119	**108**	86
	6	**174**	82	**160**	161	**122**	121	**111**	82
No. of Patients		6	6	14	13	17	16	34	35

Note: Assessments made during week on aspirin are in bold type.

practice. Assessment of the value of an analgesic agent in painful disease states is further complicated by the finding that a substantial proportion of those suffering from them may derive complete or partial relief from an inert placebo (Beecher, 1955; Lasagna Mosteller, von Felsinger, and Beecher, 1954; Traut and Passarelli, 1957; Orkin, Joseph, and Helrich, 1957) and that this "placebo effect" may have properties such as time relationship to administration similar to those of agents known to have definite analgesic potency (Lasagna, Laties, and Dohan, 1958). It seems probable that some at least of the spontaneous improvement noted between the first and second weeks in these trials may have been a "placebo effect" of admission to hospital. In the absence of a common yardstick, the problem of communication by the person experiencing it of an account of the pain such that an observer can form an accurate estimate of its severity in any absolute terms is insuperable and the best that can be achieved is an estimate of how the pain has changed during a given interval. Furthermore, when the effects of different drugs on the pain are being compared, unconscious bias on the part of the observers may seriously influence the results unless a "double blind" procedure is adopted so that both patient and observer are unaware which drug is being given at any one time.

Beecher (1957) has recently reviewed the many methods which have been devised for the clinical testing of analgesics, and some justification is necessary for the introduction of still another one. The method described is simple and can be readily incorporated in the routine management of patients admitted to hospital for treatment of inflammatory polyarthritis and is therefore suited to the screening of new analgesics which appear so frequently for use in rheumatic diseases. Administration of the drugs for a week as part of the treatment is more likely to give an idea of their relative effects in clinical practice and to induce less "trial consciousness" than methods employing frequent questioning of the patient after administration of a single dose. Restriction of the trial to new in-patients has the advantage that environmental variables can to some extent be controlled, certainty that a patient has taken the correct medication at the right times can be reasonably assured and the early signs of toxicity can be recognized. While change in grip strength over short periods of time is undoubtedly influenced by such factors as mood in addition to severity of pain; it is less influenced by these and also by similar factors operating on the observer than is the latter's interpretation of the severity of the pain from the patient's statements, and it thus provides a more objective criterion of change in pain intensity. Alternation in the order of drug administration permits estimation of the spontaneous improvement which may be appreciable in relation to the effect of medication. These trials have also shown that the method can achieve discrimination between drugs with a reasonably small number of patients.

In view of the high dosage of prednisone employed, 30 mg. per day, its superior analgesic effects as judged by this method are not surprising. The result with phenylbutazone is at variance with that obtained by Fjellström, Goldberg, Lindgren, and Nilsson (1957) in the only comparable controlled trial of which we are aware; they found a greater decrease in the number of joints tender to pressure and painful on passive motion in patients receiving phenylbutazone in addition to aspirin *ad lib.* than in those receiving aspirin *ad lib.* alone. The discrepancy may be due to their patients having received a total of 5 g. phenylbutazone in the first week as compared with 2·1 g. in this study, and to their control patients having taken a substantially lower dose of aspirin. The finding by this method that NAPAP has analgesic properties inferior to those of aspirin is in accordance with that of Orkin and others (1957), who compared the effects of 0·6 g. aspirin with those of 0·5 g. NAPAP in relieving postpartum cramps. Wallenstein and Houde (1954), whose patients were suffering from pain due to cancer, found little or no difference between equal dosages of NAPAP and aspirin. Batterman and Grossman (1955) concluded that, in patients with painful musculo-skeletal disorders of various types, with the exception of those suffering from "exudative forms of arthritis", NAPAP in comparable dosage was superior to aspirin as an analgesic. This unresponsive category of patients was not further defined, but would presumably include most patients with active inflammatory polyarthritis such as took part in the present trials.

Much publicity has attended the recent reports of the finding of occult gastro-intestinal bleeding in a high proportion of patients receiving aspirin (Stubbé, 1958; Alvarez and Summerskill, 1958; Porter, Lewis, and Dixon, 1958), but, while in occasional individuals this may result in serious anaemia (Summerskill and Alvarez, 1958), in the majority it is not a serious problem (Duthie, 1958).

The low incidence of toxicity observed with prednisone was related to the short duration of therapy in this trial, because such high dosage if given for prolonged periods, would undoubtedly be attended by serious side-effects. The low incidence of toxicity observed with phenylbutazone is also misleading, partly on account of the short duration of

therapy, but also because patients who had previously had toxic reactions or who were predisposed to toxic reactions by the nature of their disease were excluded. With NAPAP, toxic effects were observed with approximately the same frequency as with aspirin. The results of these trials would therefore support the contention that, of the agents tested, aspirin is still the most satisfactory analgesic for routine use in patients with polyarthritis of the rheumatoid type.

The principal advantage of sequential analysis over the conventional procedure, by which the number of patients in a trial is fixed independently of the results, is a saving in the number of patients required (Armitage, 1954). If a conventional fixed-sample trial is to be as effective in discriminating between drugs as the sequential procedure chosen, about forty patients would be needed (twenty receiving the medications in each order). It is assumed, of course, that apart from the sequential aspect, the trial arrangements would be the same.

In a sequential procedure, the number of patients varies from trial to trial. The average length of trials conducted according to the chosen sequential procedure cannot be precisely computed. It seems likely that the saving in patients in comparison with the conventional method will often be rather small. If the difference between the two drugs compared is roughly equal to the target difference of the sequential test, the average number of pairs of patients required would probably be about fifteen. However, data for a greater number will probably be collected, because some patients would have begun the trial when it is decided to stop further intake—and indeed there are advantages in collecting the additional data, as explained above. Under these circumstances the *average* saving in patients would be slight. If the difference between the drugs compared were about half the target difference, there would probably be no saving at all.

The main argument for sequential analysis as used in the present trials must, therefore, be the likelihood that a trial would stop early if the difference between the drugs being compared is large—considerably larger than the target difference. This advantage would be more appreciable in circumstances where the length of the corresponding fixed sample size trial is greater, *i.e.* in trials where a finer discrimination between drugs is attempted so that a greater number of patients will usually be required (this means either that more stringent significance levels are used, or a smaller target difference is chosen). For example, in relation to a fixed sample trial involving 100 patients, the advantage of a sequential method which might detect a large difference between drugs with only thirty patients is readily apparent.

Against this must be set the risk of an occasional long run. This is a more serious disadvantage than appears at first sight. In a trial of fixed size, the duration of which can be predicted with reasonable accuracy, it is possible to maintain the quality of the data. We found that the longer the trial continued the greater was the proportion of inadequate records.

Statistical methods are much better developed for conventional trials of fixed size. Hence much greater flexibility is possible both in planning and in the analysis of the results. A special disadvantage of sequential analysis is the need to use a single index. An awkward form of this difficulty is presented by toxic reactions. Patients suffering from toxic reactions serious enough to cause their withdrawal from the trial are, in the present scheme, simply left out of the sequential decision procedure. Such toxicity ought to weigh heavily against the medication presumed responsible, but it is not easy to see how to take it into account. Again, a procedure based on a single index might conceivably give misleading results if one of the drugs tested caused a withdrawal rebound in symptoms. In the worst case a drug might have little analgesic effect, though its withdrawal caused a considerable increase in symptoms. The present scheme of sequential analysis might thus make it appear a good analgesic. To some extent this difficulty is common to all methods involving the administration of drugs for short periods in succession, however they may be analysed; but, whereas detailed examination of the data might well reveal the withdrawal effect, analysis based on a single criterion might prove unsatisfactory.

The saving in the number of patients which sequential methods are designed to achieve could be more usefully exploited if two modifications could be introduced. These modifications are not within the scope of existing statistical techniques, but as statistical theory develops, both modifications may soon become feasible. In the first place the present procedure combines results for pairs of patients who received the drugs in opposite order, and ignores their separate contributions. Thus the observations collected are not fully exploited in the estimation of variability. It would be desirable to have a procedure not subject to this criticism. An approximate method devised by Rushton (1952) may supply what is needed here. This problem is part of the reason why the saving in the number of patients secured by the sequential analysis is in the present instance relatively small. Secondly, the risk of occasional long runs would be avoided

if a procedure were devised by which a fixed number* of patients is included in a trial, but with the possibility of stopping early if large differences appear. Armitage (1957) has worked out such schemes for qualitative data (*i.e.* data of the type where patients are classified as "improved" or "not improved"); he has called them restricted sequential schemes. So far no such schemes are available for trials where the observations are measurements.

The sequential analysis employed in the present trials has proved entirely practicable. However, it has serious drawbacks. In the absence of new developments in statistical theory, its advantages are outstanding only where the corresponding conventional trial would require a large number of patients and it is important to be able to stop early if the difference between the drugs considerably exceeds the "target" difference.

Summary

A method for comparing the short-term symptom-relieving properties of two drugs in patients with rheumatoid arthritis is described. By this method patients on admission to hospital receive either aspirin or the drug being compared, for one week, and the other drug in the second week. The patient is questioned at three specified times in each week regarding the severity of pain and stiffness by an observer who is unaware which medication he is receiving, and his strength of grip is recorded.

The differences between drugs were found to be largest in relation to other fluctuations when measured by grip strength, and this was used as the "index" in a sequential procedure which indicated when sufficient observations had been accumulated to determine that there was either a difference of predetermined magnitude, or no significant difference, between the effects of the drug being tested and those of aspirin. It was found that the strength of grip tended to be better in the second week in hospital than in the first week, independent of the medication, while pain and stiffness tended to be less. The effects of this spontaneous improvement may be large enough to obscure important differences between drugs. Adjustments were made for these effects in the analysis of the data.

Four substances were compared with aspirin 5 g. daily.

(1) 4-hydroxy-isophthalic acid (HIPA) 6·7 g. daily.
(2) Prednisone 30 mg. daily.
(3) Phenylbutazone 300 mg. daily.
(4) N-acetyl-p-aminophenol (NAPAP) 7·5 g. daily.

In the dosage given in these trials, prednisone was found to be greatly superior to aspirin. Phenylbutazone and aspirin were similar, while both HIPA and NAPAP were inferior to aspirin.

Data on suspected toxic reactions are reported. The toxicity of aspirin appeared fairly constant throughout the four trials, some 28 per cent. of patients reporting toxic manifestations. The toxicity of prednisone and phenylbutazone was lower than that of aspirin, in the latter case presumably because patients who gave a history of adverse reactions to phenylbutazone or who had conditions predisposing them to serious side-effects had been excluded from the trial. Toxic reactions were recorded at least as frequently for NAPAP as for aspirin.

The trial procedure described can readily be incorporated into the routine management of patients hospitalized for rheumatoid arthritis with little disturbance or additional labour. Trials of this kind seem more appropriate for evaluating the performance of analgesics in clinical practice than methods relying on intensive questioning after administration of a single dose.

The method permits useful discrimination between analgesics with a relatively small number of patients. The degree of discrimination arrived at in the present trials would take some forty patients in a trial of fixed sample size. In fact, the number of patients included varied from trial to trial, since it was determined by the sequential procedure mentioned. This has the advantage of permitting a trial to stop early if large differences appear between the effects of the drugs compared.

The disadvantages of the procedure are also discussed.

The statistical methods used are described in an Appendix.

We are greatly indebted to Prof. J. H. Kellgren for much advice in the planning of these trials which were carried out on patients under his care. These studies would have been impossible without the willing co-operation of Dr. E. J. Epstein, Dr. R. Whitaker, Dr. L. J. Atkinson, and Dr. K. D. Coorey, who were the Medical Residents during the periods of these trials, and of the Nursing Staff of the Manchester Royal Infirmary and of the Devonshire Royal Hospital, Buxton, particularly Sister Whittaker.

We are also grateful to Mr. J. C. Hanbury of Messrs.

* The idea here is that the fixed number of patients should be similar to that needed in a conventional fixed-size trial. Of course, even in sequential trials which in theory run on indefinitely, a limit has in practice to be imposed. But, if the theoretical risks of error of a sequential procedure are to be retained, it is usually necessary that the upper limit to the length of a trial be much larger than the corresponding conventional trial of fixed size.

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STATISTICAL APPENDIX

(1) The Sequential Test Used

The test employed to determine the length of the last three trials was a sequential *t*-test.

Suppose that we have a sample of patients, each of whom has been treated with two drugs, and that some index of the difference in effectiveness between the two drugs is available for each patient. To apply a conventional *t*-test, we compute the average of this index and divide it by its standard error. This ratio is then compared with a theoretical ratio from a *t*-table.

In a sequential *t*-test we perform such calculations each time that an additional observation has been obtained. At any observation we may either (*i*) stop, because we already have enough evidence for a decision (average difference very small or very large in relation to fluctuations), or (*ii*) continue the trial, because there is not yet sufficient evidence for a decision (average difference intermediate in relation to fluctuations).

In practice it is not necessary to compute explicitly the ratio of the average difference to its standard error at every step. It is more convenient to calculate a related quantity, the sequential criterion (z) defined as:

$$\frac{(\text{Sum of Observations})^2}{\text{Sum of Squares of Observations}}$$

At each stage we compute this criterion using all the observations so far accumulated as illustrated in Tables II and III. The reason why this criterion can be used is that we can find stopping limits in terms of it. There are various ways of doing this. The limits may be computed by means of an approximation developed by Rushton (1952). However, by far the easiest method of obtaining stopping limits is to look them up in a convenient set of Tables published in 1951 by the U.S. National Bureau of Standards.

These Tables list many sets of limits by which we could guide our trial procedure. To choose between them we must decide what properties our procedure is to have. We can use the Tables if we specify:

(*a*) Significance levels.*

(*b*) How big a difference (in relation to fluctuations) we want to be fairly sure of detecting; this will be called the "target" difference.

However, in order to make a choice under (*b*), we need:

(*c*) A single index to measure the difference between drugs.

The selection of procedure in all these respects involves a substantial arbitrary element.

As for (*a*) significance levels, we have retained the conventional 5 per cent.

Discussion of points (*b*) and (*c*) hinges upon the magnitude of the fluctuations† to which the observations are subject. Drug differences when measured by the chosen index must appear large in relation to the fluctuations in the index caused by other factors. Secondly, the "target" difference must be set smaller than such differences between drugs as experience has shown to be appreciable. The preliminary experiments mentioned before suggested that in terms of grip the difference between aspirin and HIPA was of the order of one standard deviation. In terms of pain and stiffness (as well as other measurements), the difference seemed considerably smaller. A larger number of patients is required to detect a smaller difference. It was, therefore, decided to use grip strength as the index for the sequential analysis, since this would make it possible to ascertain the existence of differences between drugs (or absence of difference) with the smallest number of patients. The fact that on the ratings for pain and stiffness it would be difficult for many patients to record

* In sequential *t*-tests two significance levels must be chosen:
(*i*) The probability of concluding, falsely, that there is a difference between the drugs when there is in fact none;
(*ii*) The probability of concluding falsely, that there is no difference when in fact there is a difference of the magnitude specified under (*b*).

It is not necessary that the same figure should be used for both significance levels, but we have in fact done this in the trials reported here. In a trial with fixed sample size, only the probability of errors of type (*i*) is explicitly specified in the statistical test.

† Other considerations relevant to the choice of an index are dealt with above, pp. 190 and 200.

a substantial improvement over the level reached when they are treated with aspirin, is also an argument in favour of using grip strength as an index (at least in trials where aspirin is the standard of comparison). An attempt was made (by discriminant analysis) to find a combined index of several criteria which might give better discrimination between drugs than grip strength alone. However, on the data available, the improvement over grip strength alone achieved by the best possible weighted combination of several types of observation was small, and it seemed likely that a combined index with weights fixed in advance would often be no better, if not worse, than grip alone.

Since the difference between HIPA and aspirin appeared to be about one standard deviation in terms of grip, it was felt adequate to set the "target" difference between drugs (the difference which would be detected fairly certainly, *i.e.* with 95 per cent. probability) at 0·6 of a standard deviation. It seemed from the preliminary experiments that there was little difference between HIPA and a placebo. A trial with a target difference of 0·6 standard deviation should therefore detect any medication which is as much superior to aspirin as aspirin is superior to an inert substance; it would also reveal any medication which is not much better than a placebo.

It would be tempting to set the target difference at a lower figure, *i.e.* to increase the sensitivity of the trial. However, the number of patients required increases fairly rapidly if this is done.

In accordance with these arguments it was decided to determine the length of the first sequential trial (prednisone/aspirin) by a sequential *t*-test with:

(*a*) 95 per cent. significance levels,
(*b*) A target difference of 0·6 standard deviation,
(*c*) Using a difference of grip strength as the index of the difference in drug effect.

A snag which was not entirely unexpected appeared almost at the start. A very pronounced "spontaneous improvement" effect became evident, *i.e.* the results differed strikingly according to the order in which the patient had received the drugs. To allow for this effect (otherwise the trial would have been very prolonged), it was decided to amalgamate the observations for pairs of consecutive patients such that one member of a pair received the drugs in the reverse order from the other member. The observations for the two patients in a pair were added and the sum treated as a unit for the sequential analysis, as explained in the text. The target difference was altered to 0·85 of a standard deviation. This figure for a test of sums of pairs of observations corresponds to a target difference set at 0·6 of a standard deviation for a test using individual observations.*

This procedure was retained unchanged throughout the subsequent trials. The appropriate stopping limits are given in Table III above.* It may be asked how this procedure looks in the light of the evidence on variability in the observations which has thus been accumulated. Data relating to this question are set out in Appendix Tables A and B.

APPENDIX TABLE A
STANDARD DEVIATIONS OF DIFFERENCES IN MEAN DAILY ASSESSMENTS

Assessments	Trial			
	HIPA	Prednisone	Phenylbutazone	NAPAP
Grip (mm. Hg) ..	17·7	20·9	14·1	13·1
Pain (Arbitrary rating)	0·79	0·39	0·42	0·50
Stiffness (Arbitrary rating)	0·41	0·49	0·43	0·46

Note: Figures given are the square roots of variances computed by Formula (2) below.

APPENDIX TABLE B
RATIO OF DRUG EFFECTS TO THEIR STANDARD DEVIATIONS

Assessments	Trial			
	HIPA	Prednisone	Phenylbutazone	NAPAP
Grip	1·40	0·74	0·11	0·43
Pain	0·42	0·53	0·07	0·35
Stiffness	1·03	0·24	0·07	0·18

Note: Figures in Table VI divided by corresponding figures in Table A above. Discrepancies are due to rounding.

Table A shows the standard deviations of the differences between the mean assessments in the two trial weeks. For stiffness the standard deviations in the four trials are practically identical. The figures for grip and pain show variations which are statistically significant.† There may well have been some change in the variability of the observations as the trials proceeded (for example, owing to the changes in admission practices, or differences between the observers at successive periods). Such changes as occurred seem to have been small.

Table B gives the ratios of the drug effects in Table III above to the standard deviations in Table A. The selection of grip for use in the sequential analysis is clearly justified. The drug effects as measured by grip are considerably larger in relation to the standard deviation, than as measured by pain and stiffness. The target difference of 0·6 of a standard deviation‡ (corre-

* The reason for this is that $0{\cdot}6\sqrt{2} = 0{\cdot}85$.
If pairs of independent observations whose mean is 0·6 of their standard deviation are added together, the sums will have a mean 0·85 times their standard deviation.

* The National Bureau of Standards Tables contain stopping limits for target differences of 0·8 or 0·9 standard deviations. The limits for 0·85 standard deviations can be taken to be halfway between those for 0·8 and 0·9. As it happens, the value of 0·85 was used by Armitage (1954), and the stopping limits are given in his paper.

† Bartlett's test of the homogeneity of variances, *e.g.* Quenouille (1950), gives χ^2 of 9·6, 10·7, and 0·5 for grip, pain, and stiffness respectively. With three degrees of freedom, the probabilities that these figures be exceeded are about 0·03, 0·02, and 0·95.

‡ The standard deviations involved relate to the population of observations from individual patients, not to sums of observations from pairs. Hence the figures in Table B should be compared with the target difference of 0·6 (not 0·85).

sponding to 0·85 for sums of pairs) also seems not unreasonable for detecting drug effects in terms of grip, though for NAPAP the difference seems to be below the target figure. This, and the fact that the ratio for prednisone in Table B is not very greatly in excess of 0·6, are perhaps arguments for choosing a smaller target difference.

(2) Estimation of Spontaneous Improvement

An experiment in which two drugs are given to patients in different orders may be regarded as an example of what is sometimes termed a "cross-over" design. It has been employed in many types of experimentation. Apart from other advantages, it has the merit that it is possible not only to make allowance for the order of administration of the drugs in estimating the drug effects, but also to obtain direct estimates of the effects of the order of administration, *i.e.* the spontaneous improvement. The analysis of a "cross-over" trial (*i.e.* computation of both drug effect and spontaneous improvement with standard errors, etc.) is a simple matter and within the capacity of anyone with an elementary knowledge of statistics. The procedure is therefore briefly explained here.* There is no necessary connexion between cross-over designs and sequential methods.

Suppose that two drugs X and Y are compared. If we divide the patients into groups (according to the order in which they receive the drugs) and calculate for each group the mean grip strength for each week, we might obtain the following Table:

MEAN GRIP (mm. Hg)

Week	First	Second
X-Starters	(X) 100	(Y) 150
Y-Starters	(Y) 170	(X) 160

We make the assumption that the effects of medication and spontaneous improvement add together. We can then regard the figures in the above Table as being made up of the following four factors:

(*a*) The mean grip of the X-starters over the total trial period (125).

(*b*) The mean grip of the Y-starters over the total trial period (165).

(*c*) The drug effect, *i.e.* the difference between the effects of Drug X and Drug Y.
Mean under Drug Y minus mean under Drug X=30.

(*d*) Spontaneous improvement, *i.e.* the difference between the first and second week.
Mean of second week minus mean of first week=20.

The values given in brackets will be found to fit the figures of the Table. For the X-starters, the drug effect and spontaneous improvement reinforce each other and cause a rise of 50 points between the first and second weeks. For the Y-starters, drug effect and spontaneous improvement work in opposite directions and cause a drop of 10 points (*i.e.* 30−20=10).

The individual figures in the Table may be expressed in terms of the four factors indicated. For example, the figures for the Y-starters may be represented as follows:

For the first week:

Factor (*b*) + ½ factor (*c*) − ½ factor (*d*)
i.e. 165 + 30/2 − 20/2 = 170

For the second week:

Factor (*b*) − ½ factor (*c*) + ½ factor (*d*)
i.e. 165 − 30/2 + 20/2 = 160

There are various ways of computing figures for the drug effect and spontaneous improvement from data such as those given in the Table above. One method is to take the difference between the X-week and the Y-week for each group of patients. Suppose we subtract the X-value from the Y-value, as follows:

For X-starters 150 − 100 = 50
For Y-starters 170 − 160 = 10

The drug differences and spontaneous improvement are then respectively half the sum, and half the difference between these two.

Thus:

Drug Effect = ½(50 + 10) = 30
Spontaneous Improvement = ½(50 − 10) = 20

The figures given in Table V and VI are drug effects obtained in this manner as already explained in the text.

This way of computing estimates of the drug effect and spontaneous improvement gives a clue to the random fluctuations which we may expect to occur in these estimates as trials are repeated with different groups of patients. It is seen that the *level* of grip of the patients is irrelevant, only the *difference* between the values recorded in the two trial weeks affects the estimates. Hence we can obtain standard errors for the estimates in terms of these differences.

This method of computation also indicates that the same standard errors apply for estimates of the drug effect and for estimates of spontaneous improvement. The precise formula is as follows: As above, page 191, let the observations (*i.e.* differences between the mean assessments in the two weeks for successive patients) be denoted by $x_1, x_2, \ldots$ for patients who received the drug in one order, and by $y_1, y_2, \ldots$ for patients for whom the order was reversed. Let N_x and N_y be the numbers of the two kinds of patients. We wish to estimate the variance of the estimated drug effect (or of spontaneous improvement).

If we denote the desired variance estimate by s^2, we have

$$s^2 = \frac{\sum_i (x_i - \bar{x})^2 + \sum_i (y_i - \bar{y})^2}{N_x + N_y - 2} \qquad (1)$$

The standard error may be written (using the square root s of this expression:

$$\text{Standard Error} = \frac{s}{2}\sqrt{\frac{1}{N_x} + \frac{1}{N_y}} \qquad (2)$$

$\bar{x}$ and $\bar{y}$ are the means of the x_i and y_i respectively.

* For a full technical discussion, see Fieller (1940).

For practical computation it is, of course, more convenient to replace the two expressions in the numerator of (1) by the usual short-cut formulae used in the computation of variances, *i.e.*

$$\sum_i (x_i - \bar{x})^2 = \Sigma x_i^2 - \frac{(\Sigma xi)^2}{Nx},$$

and

$$\sum_i (y_i - \bar{y})^2 = \Sigma y_i^2 - \frac{(\Sigma y_i)^2}{Ny}.$$

It may be noted that the analysis of "spontaneous improvement" can be carried out in the simple form described here only because quantitative variables are involved. The percentages which occur when the observations are qualitative (*e.g.* "improved" and "not improved") are more difficult to handle in such an analysis.

(3) Comparison between Sequential and Fixed Sample Size Tests

One difficulty with sequential *t*-tests is that it is not at present possible to compute the average sample size which would be required if trials were repeated many times under identical conditions. From the properties of other sequential tests and from sampling experiments reported in the introduction to the National Bureau of Standards Tables, one may reasonably guess that if the difference between the drugs being compared is, in fact, at the target level a trial by the procedure described would on average require about fifteen pairs of patients. Under other circumstances, the average number of patients required would be different, as explained on pp. 193 and 203 above.

How large a conventional fixed-sample trial would correspond to one using the sequential procedure selected, the trial arrangements being the same except for the sequential aspect? We assume that the trial would comprise two groups of patients (equal, or nearly equal, in number) who are given the drugs in different orders. The analysis of a trial of such design (a "cross-over" design) has been described in the previous section. The drug effects would be estimated, as in Table V above, by taking the mean of the results for the two groups. Their standard errors would be given by Formula (2) above. The ratios of the drug effects to their standard errors could be tested by a *t*-test.

If we use a 5 per cent. significance level in such a test, we secure the same chance as in the sequential procedure of wrongly concluding that there is a difference between the drugs when in fact there is none. How many patients need to be included in the trial if there is to be only a 5 per cent. chance, as in the sequential procedure, of concluding falsely that there is no difference between two drugs when this difference is in fact at the target level (*i.e.* 0·6 of a standard deviation)? The answer depends upon what is technically known as the "power" of the test used. It turns out upon investigation that about forty patients are needed, roughly twenty receiving the drugs in each order.

We may calculate the approximate precision with which the drug effects could be estimated from a fixed-sample trial involving forty patients. Confidence intervals, at the 95 per cent. level, would have a length of some 10 mm. Hg for grip strength and 0·3 points on the arbitrary rating scale for pain and stiffness. (The width of a 95 per cent. confidence interval is 3·9 times the standard error.)

No similar statement regarding the precision of estimation is possible for the sequential procedure, since the number of patients included would vary from trial to trial. Indeed, methods of estimating and of obtaining confidence intervals or other indicators of precision when the length of a trial has been determined by sequential methods are not well established (Anscombe, 1954; Armitage, 1958). It seems likely that, in the circumstances of the present trials, standard errors and the confidence intervals associated can be interpreted as if the number of patients in the trials had been fixed independently of the results.

Evaluation des analgésiques dans l'arthrite rhumatismale à l'aide d'un procédé séquentiel

Résumé

On décrit une méthode pour comparer l'effet analgésique temporaire de deux médicaments chez des malades atteints d'arthrite rhumatismale. D'après cette méthode, pendant la première semaine de leur séjour à l'hôpital, un groupe de malades était traité par l'aspirine et un autre groupe par le médicament étudié; pendant la seconde semaine on renversait le traitement dans chaque groupe. Trois fois par semaine, à des temps déterminés, un observateur qui ignorait l'identité du médicament, interrogeait les malades sur la sévérité de la douleur et de l'enraidissement et notait la force de leur poigne.

On a trouvé que la différence entre les médicaments était la plus grande, par rapport aux autres fluctuations, quand on la mesurait par la force de la poigne. On a choisi celle-ci comme "indice" dans le calcul séquentiel qui indiquait quand le nombre d'observations était suffisant pour déterminer soit une différence de magnitude prédéterminée, soit une différence insignifiante entre les effets du médicament étudié et ceux de l'aspirine. On a noté que la force de la poigne tendait à augmenter au cours de la deuxième semaine à l'hôpital, indépendamment du traitement, tandis que la douleur et l'enraidissement tendaient à diminuer. La magnitude de cette amélioration spontanée aurait pu masquer des différences importantes entre les médicaments et on en a tenu compte au moment d'analyser les données.

Quatre substances ont été comparées à 5 g. d'aspirine par jour:

(1) Acide 4-hydroxy-isophtalique (HIPA) 6,7 g. par jour.
(2) Prednisone 30 mg. par jour.
(3) Phénylbutazone 300 mg. par jour.
(4) N-acétyl-p-aminophénol (NAPAP) 7,5 g. par jour.

Aux doses administrées au cours de ces recherches, la prednisone s'est avéré très supérieure à l'aspirine. La phénylbutazone et l'aspirine étaient similaires, tandis que l'HIPA et le NAPAP étaient inférieurs à l'aspirine.

On rapporte les données concernant les réactions toxiques. La toxicité de l'aspirine était assez constante au cours des quatre expériences, et à peu près 28 pour cent des malades a révélé des manifestations toxiques. La toxicité de la prednisone et de la phénylbutazone

était inférieure à celle de l'aspirine; ceci, en ce qui concerne la phénylbutazone, peut s'expliquer par le fait que les malades avec des antécédents de réactions secondaires à ce médicament ou bien qui souffraient de désordres prédisposant à de telles réactions, ont été exclu de l'expérience. Les réactions toxiques avec la NAPAP ont été au moins aussi fréquentes qu'avec l'aspirine.

Le procédé décrit ci-dessus peut être facilement incorporé à la routine hospitalière dans les salles contenant des malades atteints d'arthrite rhumatismale, sans dérangement ou travail excessif. Des expériences de ce genre semblent être plus appropriées pour évaluer l'efficacité des analgésiques en pratique clinique, que des méthodes qui se basent sur une interrogation intensive après l'administration d'une seule dose.

Cette méthode permet une distinction pratique entre des analgésiques avec un nombre relativement petit de malades. Le dégré de distinction obtenu dans le travail présent nécessiterait à peu près quarante malades pour une expérience avec des échantillons à grandeur fixe. En réalité, le nombre de malades inclus variait d'une série à l'autre, étant déterminé par le calcul séquentiel déjà mentionné. Celui-ci offre l'avantage de pouvoir terminer rapidement une expérience aussitôt que la différence entre les effets des médicaments comparés atteigne la magnitude suffisante.

On discute aussi les inconvénients de ce procédé. La description des méthodes statistiques employées se trouve dans l'appendice.

Valoración de analgésicos en la artritis reumatoide utilizando un procedimiento secuencial

SUMARIO

Se describe un método para comparar el efecto analgésico temporario de dos medicamentos en enfermos con artritis reumatoide. Según este método, durante la primera semana en el hospital, un grupo de enfermos fué tratado con aspirina y un otro grupo con el medicamento estudiado; a la semana siguiente el tratamiento fué invertido en cada grupo. Tres veces por semana, en tiempos determinados, un observador que desconocía la identidad del medicamento, interrogaba los enfermos acerca de la severidad del dolor y de la rigidez y notaba la fuerza del empuñamiento.

Se notó que la diferencia entre los medicamentos fué mayor, en relación a otras fluctuaciones, cuando se la medía por la fuerza del empuñamiento. Esta fué elegida como "indicio" en el cálculo secuencial que indicaba el momento en que el número de observaciones era suficiente para determinar sea una diferencia de magnitud predeterminada, sea una diferencia sin importancia entre los efectos del medicamento estudiado y los de la aspirina. Fué observado, que la fuerza del empuñamiento tendía a aumentar durante la segunda semana de hospitalización, independientemente del tratamiento, mientras que el dolor y la rigidez tendían a disminuir. La magnitud de esta mejoría espontánea hubiera podido disfrazar diferencias importantes entre los medicamentos; este factor fué tenido en cuenta al analizar los datos.

Cuatro substancias fueron comparadas a 5 g. de aspirina diaria:

(1) Acido 4-hidroxi-isoftálico (HIPA) 6,7 g. diarios.
(2) Prednisona 30 mg. diarios.
(3) Fenilbutazona 300 mg. diarios.
(4) N-acetil-p-aminofenol (NAPAP) 7,5 g. diarios.

A las dosis administradas en estas investigaciones, la prednisona se mostró muy superior a la aspirina. Hubo similaridad entre los efectos de la aspirina y de la fenilbutazona, mientras que el HIPA y el NAPAP se mostraron inferiores a la aspirina.

Se relatan los datos respecto a las reacciones tóxicas. La toxicidad de la aspirina fué bastante constante en las cuatro investigaciones, y cerca de un 28 por ciento de los enfermos acusó manifestaciones tóxicas. La toxicidad de la prednisona y de la fenilbutazona fué inferior a la de la aspirina; respecto a la fenilbutazona, esto se puede explicar por el hecho de que los enfermos con antecedentes de reacciones secundarias a este medicamento o con disturbios predisponentes a tales reacciones, fueron excluidos de la investigación. Las reacciones tóxicas con el NAPAP fueron al menos tan frecuentes como con la aspirina.

El procedimiento descrito aquí se puede aplicar fácilmente en un hospital con enfermos reumáticos sin disturbio o trabajo excesivo. Investigaciones de este tipo parecen más apropiadas para valorar la eficacidad de analgésicos clínicamente, que métodos basadas en una interrogación intensiva después de la administración de una sola dosis.

Este método permite un discernimiento práctico entre analgésicos con un número relativamente pequeño de enfermos. El grado de discernimiento obtenido en el trabajo presente necesitaría aproximadamente cuarenta enfermos, en un cálculo con muestras de magnitud fija. En realidad, el número de casos incluidos fué variable en todas las series, siendo determinado por el cálculo secuencial ya mencionado. Este ofrece la ventaja de poder cortar rápidamente una serie tan pronto como las diferencias entre los efectos de los medicamentos comparados adquieran magnitud suficiente.

Se discuten también las desventajas de este procedimiento. La descripción de los métodos estadísticos empleados encuéntrase en el apéndice.

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AN IMMUNO-HISTOLOGICAL STUDY OF CONNECTIVE TISSUE

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Studies of connective tissue are germane to the investigation of the rheumatic diseases, and many different technical procedures have been used in the study of the histogenesis, metabolism, and pattern of reaction of connective tissue to noxious influences. Recently, immuno-histochemical procedures based on the method evolved by Coons and his colleagues (Coons and Kaplan, 1950; Coons, Leduc, and Kaplan, 1951) have been applied to the search for evidence of antibodies fixed to pathologically altered connective tissue and to the investigation of the antigenicity of connective tissue.

The present report concerns an immuno-histochemical analysis of connective tissue in which antibodies were used for the detection and localization of antigenically active components of connective tissue. Experiments will be described which have led to the conclusion that a difference in antigenic content enables reticulin fibres, which form the framework of the reticulo-endothelial system, and certain other connective tissue fibres, which are found in association with proliferating connective tissue, to be differentiated by immuno-histochemical means. The reagents used were antisera, prepared by injecting homogenates of human tissue into rabbits, and contained antibodies capable of combining specifically with antigenic elements in the tissue from which the homogenates were prepared. When serum globulin separated from such antisera is labelled with a fluorescent substance and then allowed to react with sections of human organs, the sites of specific fixation of labelled antibodies by their antigens are easily identified by their fluorescence when the tissue sections are examined under the fluorescence microscope. By using different preparations of antibody globulin, it is possible to differentiate some connective tissue components from others by virtue of the differing specificities of their content of antigenic material. In earlier work along these lines the sites of specific fluorescence produced in tissue sections by anti-human-glomerulus globulin labelled with fluorescein by the method of Coons and his co-workers (Coons and Kaplan, 1950) were compared with those produced in serial sections of tissue by anti-human-synovium globulin similarly labelled (Scott, 1957). An additional fluorochrome, lissamine rhodamine B 200 (R B 200), has recently been introduced (Chadwick, McEntegart, and Nairn, 1958). Since R B 200 emits an orange fluorescence and fluorescein a green fluorescence on bombardment by ultra-violet light, it is now practicable to expose tissue antigens simultaneously to two contrastingly labelled antibodies.

Materials and Methods

The basic immuno-histochemical manipulation used in the present investigation was the exposure of tissue sections to a mixture of anti-human-glomerulus globulin and anti-human-synovium globulin, each labelled with one or other of the two fluorochromes, fluorescein or R B 200.

The preparation of anti-human-glomerulus and anti-human-synovium antisera, their conjugation with fluorescein, and the preparation of tissue sections from quick-frozen unfixed blocks of tissue have already been described (Scott, 1957). The technique of conjugating antisera with R B 200 and the examination of tissue sections exposed to contrastingly labelled conjugates will be described in the report of a preliminary investigation of the use of contrastingly labelled conjugates to be published shortly.

Treatment of Tissue Sections.—Although the detection of antigens in a tissue section by labelled antibody involves an immunological process, it is convenient to use the histological term "staining" to denote both the treatment of tissue sections with conjugated antibody and the fluorescence seen in treated sections. In deciding whether staining was specific or non-specific, the criterion used was that specific staining should be prevented by pre-treatment of a tissue section with the

corresponding unconjugated antibody globulin, before its exposure to a conjugate, but not with unconjugated normal rabbit globulin.

The term inhibition is used here to refer to specific blocking by unconjugated antibody globulin of the staining produced by a conjugate.

Tests of Specificity.—These were performed in the following manner:

One of two sections from a block of quick-frozen unfixed tissue was exposed to antibody globulin for 18 hours, and the other to unconjugated normal rabbit globulin for the same period. The unconjugated globulins were rinsed off the sections with buffered saline (pH 7·0-7·2). After they had been rinsed the sections were washed for 5 minutes, excess saline was carefully removed, and the sections were exposed to the appropriate conjugate for 30-45 minutes. The conjugate was then rinsed off the sections which were washed in three changes of buffered saline. Sections were mounted in glycerol containing 10 per cent. buffered saline.

Direct Staining Experiments.—A drop of one or other of the conjugates was applied to a tissue section and allowed to react with it for 2 to 18 hours. Tests of specificity were run in parallel with direct staining experiments.

Mixed Staining Experiments.—The staining produced by a mixture containing equal parts of an anti-glomerulus globulin labelled with fluorescein (F anti-glomerulus) and an anti-synovium globulin labelled with R B 200 (R anti-synovium) was compared with that produced by a mixture containing R anti-glomerulus and F anti-synovium. In other experiments the staining produced by a mixture of the two immune globulins contrastingly labelled was compared with that produced by a mixture in which one of the immune conjugates had been replaced by a normal rabbit globulin appropriately labelled. For example, the staining produced by an F anti-glomerulus + R anti-synovium mixture was compared with that produced by an F anti-glomerulus + R normal rabbit globulin (N R G) mixture.

Cross-Inhibition Experiments.—Sections were pre-treated for 18 hours with an unconjugated anti-glomerulus globulin (or unconjugated anti-synovium globulin) and then exposed to an anti-synovium (or anti-glomerulus) conjugate.

Observations

The appearances produced as a result of mixed staining experiments are summarized in Table I. A range of colours from green through yellow to orange or orange-red was seen in sections treated with a mixture of the two antibodies contrastingly labelled, but the colour produced by a particular mixture in any one histological component of connective tissue was constant. When the various histological components of connective tissue were grouped according to the colour of their staining it became evident that there were three broad groups of tissue antigens.

TABLE I

REACTIONS OF CONNECTIVE TISSUES WITH MIXTURES OF ANTIGLOMERULUS AND ANTI-SYNOVIUM CONJUGATES

Histological Components		F anti-glomerulus + R anti-synovium	R anti-glomerulus + F anti-synovium
Basement Membranes	Renal glomeruli	G	O–R
	Thyroid acini	G	O–R
	Renal tubules	Y	O–R
Vascular Media	Muscular arteries and arterioles	G	O–R
	External iliac artery	G and Y	O and Y
	Aorta (thoracic)	Y	Y
	Pre-capillaries	O	G–Y
Reticulin	Synovial cell layer	Y–O	Y–G
	Splenic and hepatic reticulin	Y–G	Y–O
	Periacinar reticulin, thyroid gland	Y	Y
	Peritubular reticulin in kidney	as BM	Y and O
	Pericapillary reticulin	Y	Y
	Junction of media and adventitia of arteries	Y	Y
Fibrous Tissue	Fibrils in adventitia of vessels	O	G
	Fibrils amongst collagen of joint capsules	O	G
	Fibrils in synovial tissue	O	G
	Fibres in proliferating fibrous tissue	O	G
	Fibroblasts (cytoplasmic processes)	O–Y	G

G—green fluorescence
Y—yellow fluorescence
O—orange fluorescence
O-R—orange-red fluorescence
G-Y—green the predominating colour
Y-O—yellow the predominating colour
Y-G—yellow the predominating colour
O-Y—orange the predominating colour
BM—basement membranes

When mixtures of R+F anti-glomerulus or R+F anti-synovium were used, differential staining of the various components of connective tissue was not seen—all were stained yellow.

One of these groups contained antigens which were stained green by F anti-glomerulus + R anti-synovium mixtures and orange-red by R anti-glomerulus + F anti-synovium mixtures. Antigens reacting with the staining mixtures in this way were found in the renal glomerular capillaries (Figs 1 and 2) and arteriolar capillaries in the lung, the media of muscular arteries and arterioles, and the basement membrane of the acini of glands. They were also found in the vasa vasorum of the aorta, but were not present as constituents of the aortic media itself. Antigens of this group were not constantly seen in the basement membranes of renal tubules. When stained by F anti-glomerulus + R anti-synovium mixtures, the renal tubular basement membranes usually appeared yellow: thickened renal tubular basement membranes in a kidney showing changes of polyarteritis nodosa were seen, however, as thick green lines after staining by the same mixture (Fig. 3). When sections of normal kidney were stained by R anti-glomerulus + F anti-synovium mixture, the tubular basement membranes usually showed a fine orange inner membrane lying closely applied both to tubular cells and to an outer yellow membrane.

It is suggested that antigens of this group react only with antibodies present in anti-glomerulus conjugates, but not represented in antisera prepared against synovial tissue. This suggestion is based on the demonstration that renal glomerular capillaries, the basement membrane of thyroid acini, glomerular arterioles, and the media of muscular arteries, did not react with anti-synovium antibodies in direct staining experiments or in cross-inhibition experiments (Table II). Two antigenically active components are recognizable around the acini of the thyroid gland (Fig. 4). One of these, the basement membrane, reacts only with anti-glomerulus conjugates, the other, which is for convenience referred to here as periacinar reticulin, reacts with anti-glomerulus and with anti-synovium conjugates. The appearances seen after staining sections of human kidney with R anti-glomerulus + F anti-synovium mixtures suggest that a similar juxtaposition of basement membranes and peritubular reticulin occurs in relation to renal tubules. Goodman, Greenspon, and Krakower (1955), however, have produced evidence that renal tubular basement membranes contain antigens which react with antibodies to glomerular basement membranes but possess additional antigenic specificities not detected by such antibodies. Whether the basement membranes of renal tubules are identical with the basement membranes of renal glomerular capillaries or not must at present remain an open question.

Recently Krakower and Greenspon (1958) have suggested that large elastic arteries owe their ability to stimulate the production of a nephrotoxic serum to their vasa vasorum rather than to any specific constituent of the media or subendothelial tissue. This observation implies that the media of large

TABLE II

CROSS-INHIBITION EXPERIMENTS

Histological Component		Treatment of Tissue Sections			
		NRG ↓ F anti-glom.	Anti-synovium ↓ F anti-glom.	NRG ↓ F anti-syn.	Anti-glomerulus ↓ F anti-syn.
Basement Membranes	Renal glomeruli	+	+	−	−
	Thyroid acini	+	+	−	−
	Renal tubules	+	+	−	−
Vascular Media	Muscular arteries and arterioles	+	+	−	−
	Pre-capillaries	+	−	+	−
Reticulin	Synovial cell layer	+	−	+	−
	Splenic reticulin	+	−	+	−
	Periacinar reticulin thyroid gland	As BM	−	+	−
	Junction of media and adventitia of arteries	Not visible	Not visible	Not visible	Not visible
	Peritubular reticulin in kidney	As BM	−	+	−
Fibrous Tissue	Fibrils in adventitia of arteries	+	−	+	−
	Fibrils in subsynovial tissue	+	−	+	−
	Fibrils amongst collagen of joint capsules	+	−	+	−
	Fibres in proliferating fibrous tissue	+	−	+	−
	Fibroblasts (cytoplasmic processes)	+	−	+	−

+ = Specific staining present.
BM = Basement membranes.
− = Staining absent.

Sections were pre-treated with unconjugated normal rabbit globulin (NRG) or with an unconjugated portion of one of the immune globulins and then exposed to a conjugated portion of the other immune globulin.

vessels and glomerular capillary basement membranes are antigenically distinct and may perhaps bear some relation to the present observation that in the aorta the "basement membrane antigen" was found only in the vasa vasorum.

Some histological components of connective tissue were stained yellow both by F anti-glomerulus + R anti-synovium mixtures and by R anti-glomerulus + F anti-synovium mixtures. Structures reacting to the staining mixtures in this way formed the second group of antigens. Antigens of this group were found in the epithelial cells of renal glomeruli (Fig. 2), in the cell layer of the synovium, and in splenic and hepatic reticulin. They were also found at boundaries within connective tissue, in the sarcolemma of muscle, in pericapillary reticulin, and in the periacinar reticulin of the thyroid gland and pancreas, where they could be distinguished from the basement membrane. A yellow line was constantly present at the junction of the media and adventitia of muscular arteries and arterioles (Fig. 5) and immediately outside the media of "pre-capillaries", vessels in which the tunica media was present, but in which no internal elastic lamina was seen (Fig. 6). "Pre-capillaries" were especially numerous in the sub-synovial layer of synovium in which the changes of rheumatoid arthritis were present and in rheumatoid tendon nodules; they were also found in normal sub-synovium and in the tela-choroidea and choroid plexus. There was a gradual change in the nature of the media of elastic arteries as the vessels were followed peripherally. The media of the aorta contained antigens of the second group only, but the media of the external iliac artery contained antigens of the first and second groups.

The yellow staining produced in mixed staining experiments does not necessarily imply that contrastingly labelled anti-synovium and anti-glomerulus antibodies had become fixed to one antigenic component of connective tissue. Two components, one reacting with fluorescein labelled antibodies and the other reacting only with R B 200 labelled antibodies might well appear as a single yellow fibre if they happened to lie sufficiently close together. However, the results of cross-inhibition experiments (Table II) increase the probability that the yellow staining of capillaries, sarcolemma, periacinar reticulin in the thyroid, and splenic and hepatic reticulin in mixed staining experiments, was due to the fixation by those antigens of antibodies from each of the contrastingly labelled conjugates. The results of cross-inhibition experiments indicated that those structures which were stained yellow in mixed staining experiments reacted with antibodies present in both conjugates. Unconjugated anti-synovium antibodies, for example, prevented the staining of capillaries and splenic reticulin by anti-glomerulus conjugates. It is suggested, therefore, that antibodies to antigens of the second group are represented both in anti-synovium and anti-glomerulus antisera.

Antigens of the third group, which were stained green by R anti-glomerulus + F anti-synovium mixtures and orange by F anti-glomerulus + R anti-synovium mixtures, were found in vascular adventitia and in the capsule of joints, where they appeared as very fine lines closely applied to bundles of collagen. Collagen, which was readily recognized by virtue of its blue autofluorescence, did not react with either of the antibody globulins. The processes of fibroblasts in the cerebral lepto-

All photographs are fluorescence photomicrographs of unfixed tissue sections treated with fluorescent globulin solutions. They were taken on Super Anscochrome 35-mm. film.

Fig. 1.—Human kidney treated with F anti-glomerulus. Blue autofluorescence of tubule cells. All specific fluorescence is green. (Water immersion objective. Dark-ground illumination. 5-min. exposure × 160.)

Fig. 2.—Human kidney treated with a mixture of F anti-glomerulus and R anti-synovium. Specific green fluorescence in glomerular capillary basement membrane, yellow fluorescence in glomerular epithelial cells and orange fluorescence in periglomerular connective tissue. Blue autofluorescence of cells of renal tubules. (Water immersion lens. Dark-ground illumination. 7-min. exposure × 160.)

Fig. 3.—Human kidney from a case of polyarteritis nodosa treated with F anti-glomerulus + R anti-synovium. Fibrous tissue of interstitium shows specific orange fluorescence and thickened tubular basement membranes show specific green fluorescence. (Water immersion lens. Dark-ground illumination. 7-min. exposure × 240.)

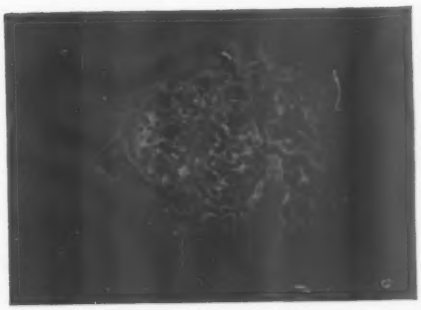
Fig. 4.—Human thyroid—a disrupted section, stained with F anti-glomerulus + R anti-synovium. The yellow periacinar reticulin has been pulled away from the green basement membrane around one acinus. (Water immersion objective. Dark-ground illumination. 3-min. exposure × 270.)

Fig. 5.—Human tela choroidea treated with R anti-glomerulus + F anti-synovium. Intima of the artery not visible. Blue autofluorescence of internal elastic lamina. Specific orange-red fluorescence of media and yellow fluorescence at junction of media and adventitia. (Water immersion lens. Dark-ground illumination. 10-min. exposure × 160.)

Fig. 6.—Human tela choroidea treated with R anti-glomerulus + F anti-synovium. A "pre-capillary" with no intima visible, specific orange fluorescence of media, yellow pericapillary reticulin. (Water immersion lens. Dark-ground illumination. 10-min. exposure × 160.)

Fig. 7.—Human leptomeninges treated with a mixture of R anti-glomerulus + F anti-synovium. Processes of fibroblasts stained green. (Water immersion objective. Dark-ground illumination. 12-min. exposure × 270.)

Fig. 8.—Human muscle—section from a case of dermatomyositis. Blue autofluorescence of muscle. Specific green fluorescence of fibrosed interstitium and specific yellow fluorescence of a thick-walled capillary. (Water immersion objective. Dark-ground illumination. 10-min. exposure × 60.)



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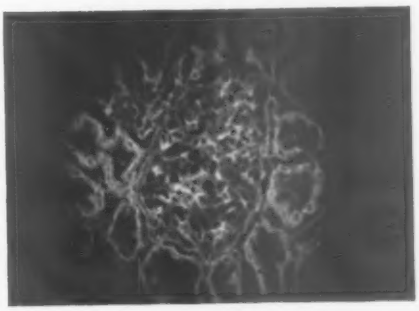

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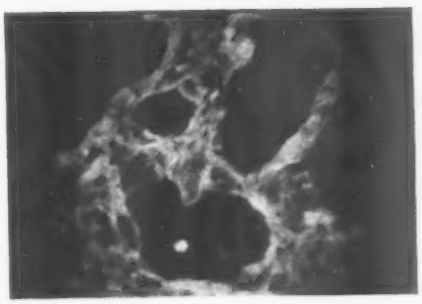

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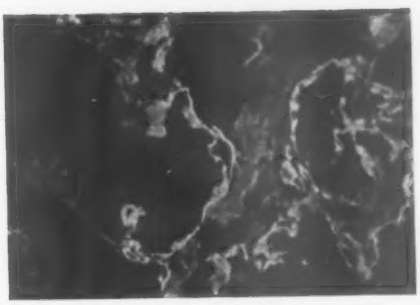

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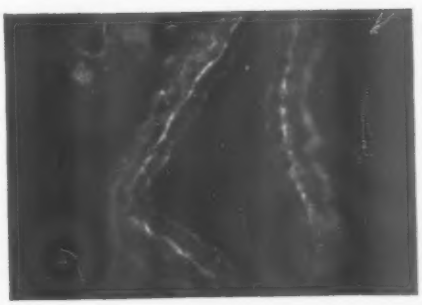

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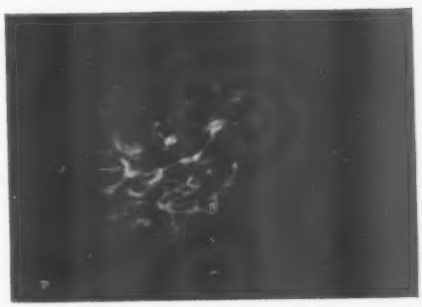

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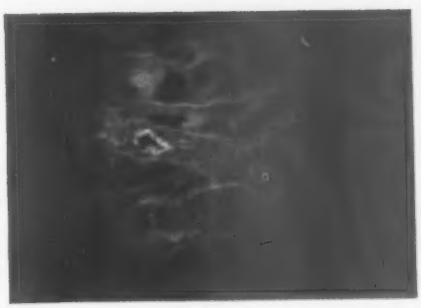

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meninges (Fig. 7) and in granulation tissue contained antigens of the third group. Green staining was produced by mixtures of R anti-glomerulus and F anti-synovium in fibrous tissue found amongst degenerated muscle bundles in a biopsy specimen from a case of dermatomyositis (Fig. 8), in sclerosed glomeruli of kidneys showing senile nephrosclerosis, and in the interstitium of a kidney showing the changes of polyarteritis nodosa (Fig. 3). Mixtures of F anti-glomerulus and R anti-synovium produced orange staining in the same sites.

Antigens of the third group, like those of the second group, were found to react with antibodies present in anti-glomerulus and anti-synovium conjugates. Antigens of these groups were stained specifically by both conjugates in direct staining experiments. In mixed staining experiments, however, antigens of the third group reacted preferentially with antibodies present in anti-synovium conjugates, whereas antigens of the second group did not. These observations suggest that antigens of the second and third groups while not antigenically identical are antigenically related. This conclusion is supported by the results of a preliminary investigation which was concerned with the techniques of the application of contrastingly labelled conjugates in immuno-histochemical studies of connective tissue, and with the interpretation of the results of experiments in which sections were exposed to two different immune conjugates contrastingly labelled. In that investigation, to be described in more detail elsewhere, anti-synovium and anti-glomerulus conjugates were found to react with splenic reticulin and with fibrils in vascular adventitia, but a difference was demonstrated in the stability of union between antigens present in vascular adventitia and antibodies present in anti-glomerulus conjugates on one hand and in anti-synovium conjugates on the other. There was no difference of this kind between the reactions of antibodies present in the two antibody globulins and antigens in splenic reticulin.

Discussion

The observations made during the course of the present investigations have been interpreted as meaning that three connective tissue antigens, or groups of antigens, can be recognized by immuno-histochemical means. For convenience these groups of antigens will be referred to as basement membrane antigens, reticulin antigens, and fibrous tissue antigens. The basement membrane antigens are distinct from the other two groups of antigens in that they react only with anti-glomerulus conjugates. The reticulin and fibrous tissue antigens react with both conjugates but differ from each other in that the fibrous tissue antigens react preferentially with anti-synovium conjugates, whereas reticulin antigens do not. The observation that anti-glomerulus conjugates reacted with reticulin does not necessarily imply that the basement membranes of renal glomeruli contain reticulin. The preparation of isolated glomeruli used for the immunization of animals contained glomerular parietal capsules as well as glomerular capillary tufts. The difference between the reaction of anti-glomerulus conjugates and anti-synovium conjugates with structures containing the fibrous tissue antigen, or antigens, might imply that the relevant anti-glomerulus antibodies were behaving as cross-reacting antibodies, but is also explicable by the postulate that traces of renal interstitium present in the crude homogenates of isolated renal glomeruli stimulated the production of antibodies having only poor combining power. The immuno-histochemical classification of connective tissue cannot be correlated with classifications based on conventional histological techniques. There is no certainty that the structures described here as basement membranes are the argyrophilic basement membranes seen in sections cut from fixed paraffin-embedded blocks of tissue. The structures detected by silver "staining" techniques may be those described here as periacinar reticulin. The difficulty usually experienced in the impregnation of renal glomerular basement membranes with silver does imply that the glomerular capillary basement membranes and other argyrophilic basement membranes of conventional histology are not identical. One of the histological criteria for reticulin is its argyrophilia and by this criterion basement membranes in general are found to contain reticulin, but the renal glomerular capillary basement membranes do not.

The classification of connective tissue by immunological methods must eventually be correlated with data obtained by chemical and physico-chemical analysis of isolated components of connective tissue. The information available at present is insufficient to permit any such correlation.

Summary

The results are reported of an immuno-histochemical analysis of connective tissue based on the use of two different antisera each labelled with one of two contrasting fluorochromes, fluorescein or lissamine rhodamine B 200.

It was found that basement membranes are antigenically distinct from reticulin on the one hand, and from a third group of connective tissue components on the other. Members of this third group

include fibroblasts, fibrils in the interstitium of organs, in vascular adventitia, in proliferating fibrous tissue, and lying between bundles of collagen in the capsule of joints. Reticulin was antigenically related to, but not antigenically identical with, members of the third group of connective tissue components.

Thus it appears that three connective tissue antigens, or groups of antigens, can be recognized by immuno-histochemical means. All three groups react with antisera prepared against human glomeruli, but only two, reticulin and the third or fibrous tissue group, react with antisera prepared against human synovium.

These findings do not necessarily imply that the renal glomerular basement membrane contains reticulin.

I wish to thank Dr. A. G. S. Hill for much helpful advice and criticism.

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Etudes immuno-histologiques du tissu conjonctif

RÉSUMÉ

On relate les résultats d'une analyse immuno-histochimique du tissu conjonctif, basée sur l'emploi de deux antisérums différents, chacun marqué par deux fluorochromes de contraste, fluorescine ou lissamine rhodamine B 200.

On a trouvé que la couche sous-épithéliale est distincte antigéniquement de la réticuline d'un coté et d'un troisième groupe de composants du tissu conjonctif de l'autre. Ce trosième groupe comprend des fibroblastes, des fibrilles dans les interstices des organes, dans la tunique adventice, dans le tissu fibreux proliférant et situées entre des faisceaux de collagène, dans la capsule articulaire. Du point de vue antigénique, la réticuline était associée mais non pas identique aux éléments du troisième groupe de composants du tissu conjonctif.

Il semble donc, qu'on peut reconnaître par des moyens immuno-histochimiques, trois antigènes, ou groupes d'antigènes, du tissu conjonctif. Tous les trois groupes réagissent avec des antisérums préparés contre des glomérules humains, mais deux seulement d'entre eux, la réticuline et le troisième ou celui de tissu fibreux, réagissent avec des antisérums préparés contre la synoviale humaine.

Ces résultats n'impliquent pas nécessairement que la couche sous-épithéliale glomérulaire rénale contienne de la réticuline.

Investigación imuno-histoquimica del tejido conjuntivo

SUMARIO

Se relatan los resultados de un análisis imuno-histoquímico del tejido conjuntivo, basado en el empleo de dos antisueros diferentes, ambos marcados por dos fluorocromos de contraste, fluorescina o *lissamine rhodamine B* 200.

Se halló que la capa sub-epitelial se distingue antigenicamente de la reticulina por un lado y de un tercer grupo de componentes del tejido conjuntivo por el otro. El tercer grupo contiene fibroblastos, fibrillas en los intersticos de órganos, en la adventicia, en el tejido fibroso proliferante y, entre fasciculos de colágeno, en la cápsula articular. Desde el punto de vista antigénico, la reticulina fué asociada pero no idéntica con los elementos del tercer grupo de componentes del tejido conjuntivo.

Parece pues, que por medios imuno-histoquimicos se pueden reconocer tres antigenos, o grupos de antígenos, del tejido conjuntivo. Los tres grupos reaccionan con antisueros preparados contra glomérulos humanos, pero tan sólo dos, la reticulina y el tercer grupo, él de tejido fibroso, reacciona con antisueros preparados contra la sinovia humana.

Estos resultados no implican necesariamente que la capa sub-epitelial glomerular renal contenga reticulina.

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SERUM COMPLEMENT, RHEUMATOID FACTOR, AND OTHER SERUM PROTEINS IN RHEUMATOID DISEASE AND SYSTEMIC LUPUS ERYTHEMATOSUS

BY

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Several authors have reported serum complement changes in rheumatoid arthritis (Rachmilewitz and Silberstein, 1937; Vaughan, Bayles, and Favour, 1951a; Kellett, 1954), and have variously found low, normal, or high levels in different cases. More recently, Williams and Law (1958) have investigated serum complement changes in a variety of "connective tissue disorders", and have found that, in a group of 48 patients suffering from rheumatoid arthritis, the complement values were always high or within the normal range.

There are several possibilities which might explain these different findings. First, a variety of different diseases may be responsible for the clinical picture of "rheumatoid arthritis" and each of these may be associated with a different concentration of serum complement. One such example is systemic lupus erythematosus, where "rheumatoid arthritis" may be the prominent clinical manifestation and may lead to a mistaken diagnosis. It is known that serum complement levels may be low in systemic lupus erythematosus when estimated by haemolytic methods (Vaughan, Bayles, and Favour, 1951b; Elliott and Mathieson, 1953; Ellis and Walton, 1958; Williams and Law, 1958), and this might explain the low levels encountered in certain cases of "rheumatoid arthritis".

Secondly, the lowering of serum complement observed in certain instances may be a relative one due to the effect of anticomplementary substances in the serum. It has not previously been possible to estimate complement activity independently of any such anticomplementary influence, as only haemolytic methods for the estimation of serum complement have been available. Recently, Ellis and Gell (1958) have described a method for the estimation of one component of complement by a gel-diffusion precipitin technique which is independent of haemolytic activity and hence not influenced by anticomplementary substances in the serum.

It was therefore decided to investigate serum complement changes in a series of patients suffering from rheumatoid disease and systemic lupus erythematosus. In addition, a miscellaneous group comprising cases of scleroderma, dermatomyositis, and polyarteritis nodosa has been studied. It was hoped, by utilizing both the haemolytic and gel-diffusion precipitin techniques, together with studies of anticomplementary activity, that conclusions could be reached regarding the absolute variations in serum complement activity in these conditions. Parallel studies of serum protein changes and the rheumatoid factor have been made.

Materials and Methods

Estimation of Serum Complement.—Titrations were made in a standardized haemolytic system and the 50 per cent. haemolysis end point was obtained from the linear graph relating the percentage haemolysis (converted into probit units) to the reciprocal of the corresponding serum dilution. A lyophilized standard reference serum was titrated in parallel with all sera to avoid errors arising from the use of different batches of sheep cells. The techniques used for the collection, handling, and storage of sera and details of this method have been previously described (Walton and Ellis, 1958). Estimations in a control series of 143 subjects gave values ranging from 0·95 to 2·05 units per ml. serum, with a mean of 1·43 units and a standard deviation of 0·27.

Estimation of Serum Anticomplementary Activity.—Anticomplementary activity of sera was determined using heat inactivated sera (56° C. for 20 minutes). Sera so treated were added in various dilutions to a 1 in 10 dilution of a standard lyophilized human serum and sensitized sheep cells. The 50 per cent. haemolysis end point was obtained by relating the percentage inhibition of haemolysis to the logarithm of the concentration of test serum. This method was based on that previously described (Walton, Ellis, and Taylor, 1957) for the estimation of the anticomplementary activity of sulphated polysaccharides.

Estimation of a Component of Complement (C_1^1).—A rabbit antiserum to a component of human complement was prepared and a gel-diffusion precipitin technique (Gell, 1957) was used for the semi-quantitative estimation of this component in test sera as previously described (Ellis and Gell, 1958). Evidence now available suggests that this is the first component of complement, hereafter denoted as C_1^1. Values for unknown sera were expressed as a percentage of a standard reference serum obtained from a healthy subject. Estimations in a control group of twenty healthy young adults gave values ranging from 87 to 150 per cent. (mean 111·8, standard deviation 18·8).

Demonstration of the "Rheumatoid Factor".—The "rheumatoid factor" was demonstrated by Ball's modification of the sensitized sheep-cell agglutination test of Rose-Waaler (Ball, 1950), but using the pattern of sedimentation in plastic cups as the index of agglutination. In addition, a ring-precipitin test in agar was used, the antigen being an 0·6 per cent. solution of human pooled gamma globulin (Lister Institute), denatured by heating at 63° C. for ten minutes.

Estimation of Serum Proteins.—Total serum proteins were estimated by the Biuret method. Albumin and the individual globulin components were estimated by means of quantitative paper electrophoresis as described by Hardwicke (1954).

Classification of Cases Studied

Rheumatoid Disease.—It was considered of major importance at the outset to exclude all patients in whom the diagnosis of rheumatoid disease was doubtful. Criteria adopted for inclusion were based upon those described by Ropes, Bennett, Cobb, Jacox, and Jessar (1957), and correspond to the "Definite Rheumatoid Arthritis" group recommended in the 1958 revision of diagnostic criteria for rheumatoid arthritis by the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959).

Cases were unselected in that they consisted of consecutive patients seen at the out-patients departments or wards in the United Birmingham and Birmingham Regional Hospitals. Over 100 cases of rheumatoid disease were originally studied, but in only 78 was the data adequate confidently to make the diagnosis for the present purpose. Cases were further subdivided into four groups, depending upon the stage of the disease (Steinbrocker, Traeger, and Batterman, 1949); Stage I, Early; Stage II, Moderate; Stage III, Severe; Stage IV, Terminal.

Systemic Lupus Erythematosus.—Eighteen cases of lupus erythematosus were studied (15 female and 3 male), of which fourteen had a widespread systemic involvement, two predominant polyarthritis and two mainly cutaneous manifestations. A total of fifteen had arthritis, nine cutaneous lesions, and eight renal involvement. L.E. cells (Hargraves, Richmond, and Morton, 1948) were found in seventeen of the eighteen cases.

Miscellaneous Group.—A limited number of miscellaneous disorders—Still's disease (2 cases), scleroderma (3 cases), dermatomyositis (1 case), and polyarteritis nodosa (4 cases)—was examined.

Results

(1) Patients with Rheumatoid Disease

(*a*) *Serum Complement.*—Estimations by the haemolytic method were made in 78 different patients at various stages of rheumatoid activity and in some instances repeated estimations were made. The results of the first value obtained in each case studied, together with the corresponding sheep-cell agglutination titre, rheumatoid factor precipitin titre, and serum gamma globulin level, are shown in Table I (opposite).

The mean serum complement value for all cases is 1·72 units per ml. (standard deviation 0·32). Comparison of this mean with the control group mean reveals a significant difference ($P < 0·001$).

Fig. 1 (overleaf) shows that, although the mean complement level is raised and many patients have raised serum complement values, many more are within the normal range. It is therefore clear that an isolated value obtained in a single patient is not likely to be of diagnostic significance. It is of interest that one patient (Case 15, Table I) had a very low value quite distinct from that obtained in the others. This is probably explained by the fact that the serum in this instance was markedly anti-complementary—sufficiently so to produce a calculated overall serum complement level of the order actually obtained. (A 1 in 12 dilution of the patient's serum produced 50 per cent. inhibition of a 1 in 10 dilution of normal serum at the time the patient's serum complement was 0·45 units per ml.) Confirmatory evidence was obtained by using the gel-diffusion precipitin technique for the estimation of the C_1^1 component of complement which gave a normal value of 100 per cent. Furthermore, serial observations over a period of many months in this patient showed a gradual rise in serum complement activity from 0·11 to 0·85 units per ml. (as measured by the haemolytic method) and a loss of anticomplementary activity, but no change in the gel-diffusion precipitin C_1^1 value which remained at 87 to 100 per cent. One can therefore conclude that, in this patient, the initial low serum complement

TABLE I

SERUM COMPLEMENT, SHEEP-CELL AGGLUTINATION TESTS, AND GAMMA GLOBULIN LEVELS IN 78 CASES

Stage of Disease	Case No.	Serum Complement (Units per ml.)	Sheep-Cell Agglutination Titre (Reciprocal)	Precipitin Test Titre (Reciprocal)	Serum Gamma-Globulin (g. per cent.)
I	5	1·28	0	0	1·22
	10	1·81	128	20	2·08
	20	1·95	0	0	1·35
	24	1·96	0	0	1·00
	31	1·83	0	0	1·90
	37	1·59	32	—	—
	38	2·49	0	0	1·54
	39	2·18	0	0	1·65
	42	1·67	0	0	0·99
	76	1·87	0	0	—
	77	2·10	0	0	—
	78	2·05	0	0	—
II	7	1·79	0	0	1·54
	11	1·61	128	10	0·80
	17	1·46	256	20	0·68
	23	2·42	0	0	1·53
	25	1·40	—	20	1·10
	28	2·50	0	0	2·78
	29	2·64	0	0	2·33
	32	2·01	16	0	1·39
	41	1·56	128	10	1·27
	47	1·72	0	0	1·73
	49	1·93	0	0	2·46
	51	1·92	0	0	2·10
	52	1·36	512	10	1·66
	53	1·50	512	0	1·41
	54	1·59	512	10	1·29
	55	1·55	32	0	2·00
	57	1·47	0	0	0·90
	60	1·78	16	2	2·04
	63	1·65	512	16	—
	67	1·93	128	4	—
	71	1·78	64	8	—
	43	1·72	32	—	—
	73	1·52	256	16	—
III	1	1·35	512	16	1·41
	6	1·41	64	0	1·61
	13	1·72	64	5	1·89
	18	1·89	256	10	1·35
	19	1·40	1,024	40	1·61
	33	1·68	0	0	—
	34	1·09	256	8	—
	35	1·89	1,024	10	2·43
	36	2·00	0	0	1·26
	44	1·55	512	20	1·57
	45	1·98	256	10	1·14
	50	1·70	0	0	1·66
	56	1·57	0	0	1·50
	58	1·50	256	2	1·61
	59	1·68	0	0	1·92
	61	1·46	32	0	1·70
	62	1·19	128	0	0·58
	65	1·80	0	20	2·13
	66	2·20	512	—	—
	68	1·03	4,096	64	—
	74	1·82	128	2	—
	75	1·50	8,192	32	—
	76	1·55	64	0	—
	77	1·13	512	8	—
IV	2	1·45	256	10	1·37
	3	2·21	512	10	1·42
	4	1·92	512	32	1·89
	8	1·90	64	8	1·39
	9	1·54	64	20	1·08
	12	1·69	0	0	2·15
	15*	0·11	1,024	40	1·75
	16	1·63	128	0	3·10
	21	1·35	0	0	1·43
	22	1·64	512	10	1·23
	26	1·74	0	0	2·90
	27	2·16	32	2	1·76
	30	1·47	128	10	2·27
	40	1·91	256	10	2·20
	46	1·57	128	10	2·00
	64	1·54	512	20	1·24
	69	1·33	512	4	—
	70	1·65	2,048	16	—
	72	1·91	1,024	8	—

* Serum markedly anticomplementary. This case was excluded from the analysed data and from Fig. 1.

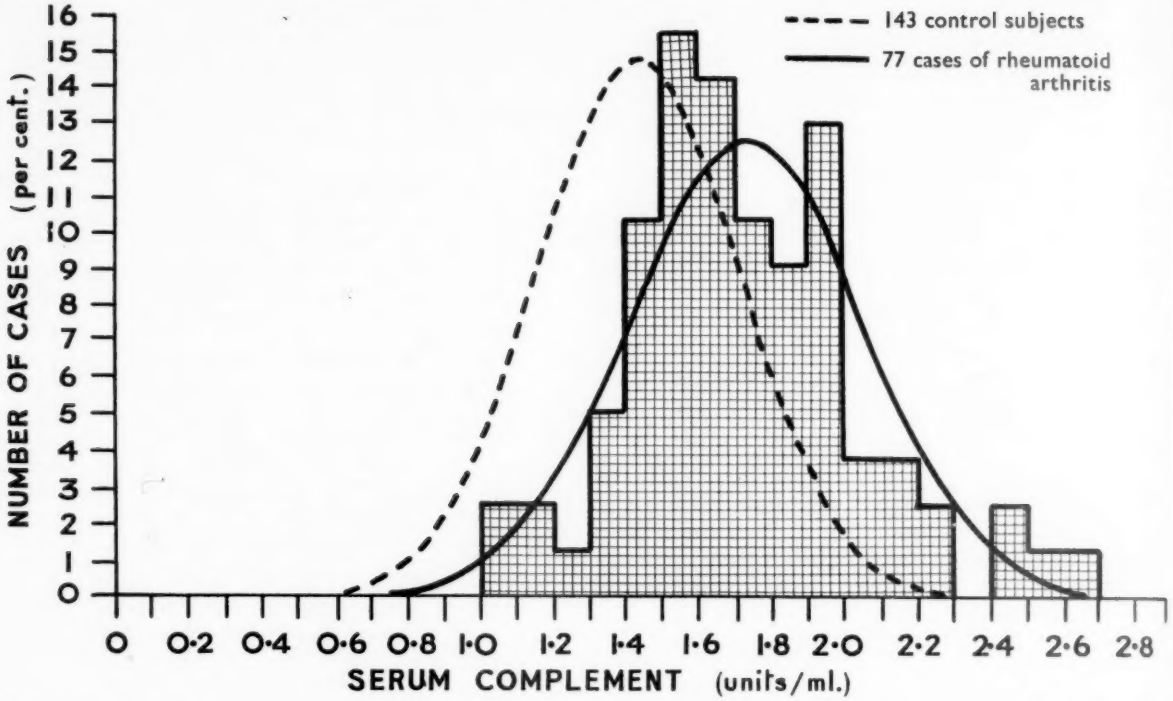
143 control subjects
77 cases of rheumatoid arthritis
NUMBER OF CASES (per cent.)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
0 0·2 0·4 0·6 0·8 1·0 1·2 1·4 1·6 1·8 2·0 2·2 2·4 2·6 2·8
SERUM COMPLEMENT (units/ml.)

Fig. 1.—Distribution of serum complement in 77 cases of rheumatoid disease (Superimposed interrupted and continuous curves represent calculated normal distributions for 143 control subjects and 77 cases of rheumatoid disease, respectively).

value was not due to an absolute reduction. No other case of rheumatoid disease had a serum which was significantly anticomplementary.

The C_1^1 component of complement was estimated in a further twenty cases of rheumatoid disease and the values obtained ranged from 75 to 200 per cent. when compared with the reference serum (mean 145 per cent., standard deviation 43 per cent.). Comparison of this mean with that of the control group confirms that there is a significant elevation of the C_1^1 component in rheumatoid disease ($P < 0{\cdot}01$).

All cases of rheumatoid disease were subdivided into the four stages previously described. The results obtained are summarized in Tables IIA and IIB (opposite), which show that there is an overall tendency for the serum complement to become less elevated in successive stages (correlation coefficient $(r) = -0{\cdot}241$; $P < 0{\cdot}05$, $> 0{\cdot}02$). This suggests that serum complement is elevated during the earlier stages of rheumatoid disease, but returns towards the normal range as the disease progresses.

(*b*) *Variations in Serum Gamma Globulin Levels.*—The levels were estimated in 58 cases, and 67 per cent. were found to have a value above the upper limit of normal (1·4 g. per cent.). Elevated levels occur in 50, 61, 75, and 73 per cent. of cases in Stages I, II, III, and IV respectively. There is also a tendency towards a higher serum gamma globulin level in successive stages (correlation coefficient $(r) = +0{\cdot}226$, $P < 0{\cdot}10$, $> 0{\cdot}05$).

(*c*) *Sensitized Sheep-cell Agglutination.*—64·1 per cent. of patients have positive sensitized sheep-cell agglutination tests; 16·7, 60·9, 75, and 84·2 per cent. in Stages I, II, III, and IV respectively. There is a significant positive correlation between the sensitized sheep-cell agglutination titres and the four stages of disease activity (correlation coefficient $(r) = +0{\cdot}394$; $P < 0{\cdot}001$).

There is also a significant negative correlation between this factor and serum complement activity ($r = -0{\cdot}557$; $P < 0{\cdot}001$). This is not necessarily a causal relationship, but supports the concept that serum complement is less markedly elevated in the advanced stages of the disease whilst the rheumatoid factor is increased.

(*d*) *Precipitin Test for Rheumatoid Factor.*—Although fewer positive results were obtained with this test, the distribution pattern follows that for the sensitized sheep-cell agglutination. 53·9 per cent. of cases have positive tests; 8·3, 50·0, 60·9, and 78·9

TABLE IIA

SERUM COMPLEMENT IN THE FOUR STAGES OF RHEUMATOID DISEASE AND IN THE CONTROL GROUP

Group of Patients			No. of Cases	Serum Complement (units per ml.)		
				Mean	Range	Standard Deviation
Rheumatoid	Stage of Disease	I	12	1·90	1·28–2·49	0·31
		II	23	1·77	1·36–2·64	0·35
		III	24	1·59	1·03–2·20	0·30
		IV	18	1·70	1·33–2·21	0·26
	All Combined		77	1·72	1·03–2·64	0·32
Control			143	1·43	0·95–2·05	0·27

TABLE IIB

SERUM COMPLEMENT AND RHEUMATOID FACTOR IN THE FOUR STAGES OF RHEUMATOID DISEASE

Correlations Examined	Total Number of Observations (n)	Coefficient (r)	(P)
Serum Complement and Stage of Disease	77	−0·241	<0·05 >0·02
Serum Gamma-Globulin and Stage of Disease	58	+0·226	<0·10 >0·05
Rheumatoid Factor* (Sensitized Sheep-cell Agglutination) and Stage of Disease	76	+0·394	<0·001
Rheumatoid Factor* (Precipitin Test) and Stage of Disease	75	+0·320	<0·01
Serum Complement and Rheumatoid Factor* (Sensitized Sheep-cell Agglutination)	76	−0·557	<0·001
Serum Complement and Rheumatoid Factor* (Precipitin Test)	74	−0·712	<0·001

* Reciprocal of serum dilutions in the sensitized sheep-cell agglutination and precipitin tests, transformed to a logarithmic scale for calculation of correlation coefficients.

per cent. in Stages I, II, III and IV, respectively ($r = +0·320$; $P < 0·01$).

A significant negative correlation also exists between serum complement and rheumatoid factor estimated by this technique ($r = -0·712$; $P < 0·001$). See Table IIB.

(2) Patients with Systemic Lupus Erythematosus

(*a*) *Serum Complement.*—This was estimated in eighteen patients with systemic lupus erythematosus (Table III, overleaf).

The values obtained varied from zero serum complement activity to 1·73 units per ml. The distribution is further illustrated and compared with the control group distribution in Fig. 2 (overleaf).

Cases 91, 92, and 93 were receiving steroid therapy and were in remission at the time of study. The remaining patients were active, although several had been under treatment with steroids for varying periods of time (see Table III for details).

Excluding the three inactive cases, the values obtained ranged from zero to 1·31 units per ml. (mean 0·56, a standard deviation 0·47). This mean is significantly different from that of the control group ($P < 0·001$).

Nine patients had a serum which was anticomplementary, and this was most marked in Cases 82, 83, 85, and 87, with serum complement values of zero, 0·08, and 0·11 units per ml. respectively. The degree of anticomplementary activity, however, did not appear to be sufficient to account for all the serum complement depression. Estimations of the $C_1{}^1$ component by the gel-diffusion precipitin technique in six cases gave low values (see Table III) from 6 to 62 per cent., except in Case 90 (150 per cent.). This shows that there is an absolute reduction in complement concentration in systemic lupus erythematosus.

Complement was found to be low in systemic lupus erythematosus whichever system was clinically predominantly affected. For example, comparable values were obtained in Case 85 (predominant cutaneous lesions), Case 83 (joint, renal, and cardiovascular lesions, but no cutaneous manifestations),

TABLE III

CLINICAL DETAILS OF EIGHTEEN CASES OF SYSTEMIC LUPUS ERYTHEMATOSUS

Case No.	Sex	Age	Main Clinical Features	L.E.-Cell Test	Serum Complement		Remarks
					Haemolytic Method (C^1) (units per ml.)	Gel-Diffusion Method ($C_1{}^1$) (per cent.)	
79	F	36	Polyarthritis, Raynaud's Phenomenon, Nephritis, Fever No Cutaneous Lesions	Positive	0·70		Serum Anticomplementary Had received ACTH for One week
80	F	37	Polyarthritis, Facial Rash, Nephrotic Syndrome	Positive	0·18		Serum Anticomplementary Not on Steroids
81	F	35	Polyarthritis, Facial Rash, Nephrotic Syndrome	Positive	0·30	50	Serum Anticomplementary On Cortisone Active
82	F	66	Polyarthritis Cutaneous Lesions Face and Digits	Negative	0		Serum Anticomplementary On Cortisone Active
83	F	46	Polyarthritis, Pericarditis, Pleurisy No Cutaneous Lesions	Positive	0		Serum Anticomplementary Not on Steroids
84	F	47	Polyarthritis No Renal or Cutaneous Lesions	Positive	1·10		Serum not Anticomplementary Not on Steroids
85	F	39	Cutaneous Lesions Face and Digits Polyarthritis No Renal Involvement	Positive	0·08		Serum Anticomplementary Not on Steroids
86	F	33	Polyarthritis, Raynaud's Phenomenon, Lung involvement	Positive	0·73	25	Serum not Anticomplementary Not on Steroids
87	M	28	Presented as Pyrexia of Unknown Origin Renal Involvement No Arthritis or Cutaneous Lesions	Positive	0·11	6	Serum Anticomplementary Not on Steroids
88	M	46	Polyarthritis, Renal Involvement No Cutaneous Lesions	Positive	0·50		Serum Anticomplementary On Steroids Active
89	F	34	Polyarthritis, Pleurisy No Cutaneous or Renal Lesions	Positive	1·03		Serum not Anticomplementary Not on Steroids
90	M	53	Polyarthritis, Pleurisy, Pericarditis, Peripheral Neuritis, Raynaud's Phenomenon	Positive	1·31	150	Serum not Anticomplementary On Steroids Active
91	F	29	Polyarthritis, Cutaneous and Renal Lesions	Positive	1·73		Serum not Anticomplementary On Steroids Inactive
92	F	33	Cutaneous Lesions Face and Digits, Pericarditis, Pleurisy	Positive	1·65		Serum not Anticomplementary On Steroids Inactive
93	F	35	Polyarthritis No Renal or Cutaneous Lesions	Positive	1·51		Serum not Anticomplementary On Steroids Inactive
94	F	32	Polyarthritis, Facial Rash, Pleurisy, Renal Involvement	Positive	1·08		Serum not Anticomplementary On Steroids Active
95	F	50	Pulmonary and Renal Involvement No Arthritis or Cutaneous Lesions	Positive	0·10	37	Serum Anticomplementary Not on Steroids Active
96	F	64	Cutaneous Lesions, Pleurisy No Arthritis or Renal Involvement	Positive	1·19	62	Serum not Anticomplementary

and Case 87 (severe widespread involvement except in the joints). It is possible that Case 84 should be regarded as one of rheumatoid disease with a positive L.E.-cell test; if so, the normal complement value would support this. On the other hand, Case 90 had a normal complement value whilst suffering from undoubted active systemic lupus erythematosus, although this patient had been receiving steroids for 2 years. The highest complement value obtained in an untreated active case of systemic lupus erythematosus was 1·03 units per ml. (Case 89, Table III).

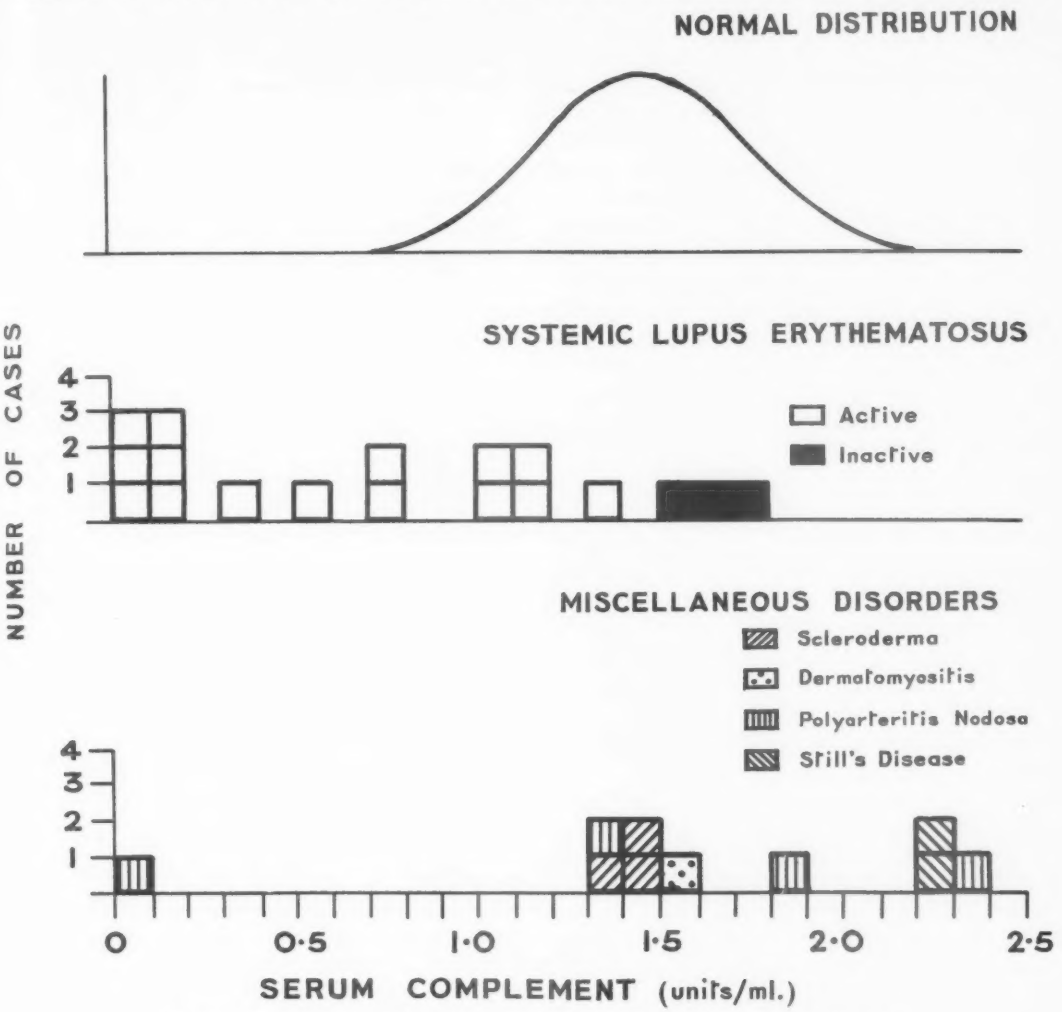

Fig. 2.—Serum complement levels in systemic lupus erythematosus and other disorders.

(*b*) *Changes in Serum Gamma Globulin.*—In twelve cases the serum proteins were studied by the quantitative paper electrophoresis technique. The gamma globulin was found to be almost consistently elevated, values ranging from 1·2 to 4·6 g. per cent. (upper limit of normal 1·4 g. per cent.). There was, however, no significant correlation between the levels of albumin or individual globulin components and those of serum complement.

(*c*) *Serial Changes in Serum Complement.*—Case 84 (Table III) was followed for one year. There was a remarkable clinical recovery in response to intensive cortisone therapy and the serum complement rose from 0·11 to 0·96 units per ml. The serum anticomplementary activity gradually diminished and there was also a rise in the C_1^1 component measured by the gel-diffusion precipitin technique. This case has been previously described and illustrated (see Ellis and Walton, 1958, Fig. 6).

(3) Miscellaneous Disorders

(*a*) *Still's Disease.*—Serum complement was estimated in two cases and high values (2·23 and 2·25 units per ml.) were obtained. One case was complicated by secondary amyloidosis.

(*b*) *Scleroderma and Dermatomyositis.*—Three cases of scleroderma were found to have values within the normal range (1·40, 1·30, and 1·40 units per ml.). A single case of dermatomyositis also had a normal value at 1·51 units per ml.

(*c*) *Polyarteritis Nodosa.*—In three cases, values

of 1·35, 1·83, and 2·38 units per ml. respectively were obtained. In the fourth case, with marked renal involvement, there was a considerable depression of serum complement activity when measured by the haemolytic method (0·05 units per ml.). After the serum had been kept at 4° C., a cryoglobulin (Lerner and Watson, 1947) separated. This cryoglobulin was actively anticomplementary, and the serum showed a rise in complement activity when it was removed. Furthermore, when it was added to normal serum, a depression in complement activity occurred. A normal value was obtained in this case for the C_1^1 component of complement estimated by the gel-diffusion precipitin technique.

The results obtained in the miscellaneous group are illustrated in Fig. 2.

Discussion

The finding of a raised serum complement level in rheumatoid disease by both the haemolytic and the precipitin methods lends further support to the findings of Vaughan, Bayles, and Favour (1951a), and Williams and Law (1958). In the single case with a depressed serum complement level (as measured by the haemolytic method), it was possible to demonstrate that this was not an absolute lowering but an apparent one brought about by the presence of an anticomplementary substance in the serum. The new gel-diffusion precipitin technique for the estimation of the C_1^1 component of human complement, independently of anticomplementary activity, proved to be of particular value in this instance.

In the active untreated cases of systemic lupus erythematosus studied, it was confirmed that serum complement was low. By utilizing the gel-diffusion precipitin technique for the estimation of the C_1^1 component, it was possible to demonstrate that, although several of the sera were anticomplementary, there was a true reduction in serum complement concentration.

Of the miscellaneous cases studied, the two patients with Still's disease had high values, and the three with scleroderma and one with dermatomyositis had normal values. Two cases of polyarteritis nodosa had normal values and a third an elevated one. A fourth was unusual in that there was relative reduction in complement due to the presence of an anticomplementary cryoglobulin.

Diagnostic Value of Serum Complement

Although one can demonstrate a significant elevation in the mean serum complement in rheumatoid disease, many individual cases have values falling within the normal range. For this reason such estimations have a limited diagnostic value. On the other hand, the finding of a low serum complement supports a diagnosis of systemic lupus erythematosus, though it is not diagnostic. In acute nephritis, for example, it is well known that serum complement is depressed (Gunn, 1914-15; Kellett, 1936; Reader, 1948; Ellis and Walton, 1958). The value obtained must therefore be interpreted in relation to the clinical features and the other laboratory data.

Complement Determinations and the Control of Corticosteroid Therapy

Serial observations of serum complement in rheumatoid disease have no obvious value in the management of patients. Such observations are, however, useful in systemic lupus erythematosus, where there is an initial low serum complement. A rise in complement after steroid therapy can occur before there are other signs of improvement, and a persistently low level in a case treated with steroids may be an indication that dosage is inadequate. Repeated estimations are therefore useful in occasional cases when a decision has to be made on a level of dosage or the duration of its administration.

Mechanisms of Complement Variation

Little is known concerning the mechanism of variations in serum complement in different disease states. An increase in activity in rheumatoid disease may be interpreted as a non-specific phenomenon occurring in response to the inflammatory process. High levels are similarly found in cases of erysipelas, scarlet fever and pneumococcal infections (Ecker, Seifter, Dozois, and Barr, 1946). Furthermore, the tissue damage need not necessarily be of infective origin, for raised levels have also been reported in myocardial infarction (Boltax and Fischel, 1956). The elevation of levels in rheumatoid disease cannot represent a fixation of complement by antigen-antibody reactions *in vivo*. Nevertheless, this does not necessarily preclude an underlying immunological mechanism.

The low levels which are found in systemic lupus erythematosus theoretically might occur as a result of three different mechanisms:

(*i*) Diminished production;

(*ii*) Interaction with circulating anticomplementary substances;

(*iii*) Increased utilization, in particular in immune reactions.

Diminished production is of course possible, but little is known of the method of formation of complement in health or disease.

With regard to the lowering of serum complement by anticomplementary substances, it has been possible in the present study to demonstrate that in systemic lupus erythematosus, although the serum may be anticomplementary, there is also a true reduction in serum complement. However, anticomplementary activity played the major part in the apparent lowering of serum complement in one case of rheumatoid disease (Case 15, Table I), and in the case of polyarteritis nodosa with cryoglobulinaemia.

The third hypothesis, that of excessive utilization, is an attractive one and is consistent with current knowledge of immune reactions in systemic lupus erythematosus. It is known that complement may be fixed during the interaction of antigen and antibody *in vivo* (Stavitsky, Hackel, and Heymann, 1954) and depressions of serum complement activity have been observed in serum sickness and penicillin reactions (Elliott and Mathieson, 1953). It appears to be established that the L.E.-cell phenomenon itself is due to the presence of an auto-antibody directed against the leucocyte nucleus (Nathan and Snapper, 1958). By the use of the fluorescent antibody technique it has been shown that sera from patients with lupus erythematosus contain an abnormal gamma globulin which combines with intranuclear deoxyribonucleoprotein (Holborow, Weir, and Johnson, 1957; Bardawil, Toy, Galins, and Bayles, 1958). Furthermore, complement fixation has been shown to occur during the reaction of the serum gamma globulin component with cell nuclei, nucleoproteins and deoxyribonucleic acid in patients suffering from lupus erythematosus (Robbins, Holman, Deicher, and Kunkel, 1957; Pearson, Craddock, and Simmons, 1958). The lowering of complement *in vivo* might therefore result from these widespread antigen-antibody reactions occurring throughout the small blood vessels of the affected organs (Dameshek, 1958).

The Rheumatoid Factor and its Relation to Serum Complement

Since Cecil, Nicholls, and Stainsby (1930) first observed that the sera from patients with rheumatoid arthritis were capable of agglutinating streptococci, much progress has been made in our knowledge of the responsible "rheumatoid factor". We have used Ball's modification of the Rose-Waaler Test (Waaler, 1940; Rose, Ragan, Pearce, and Lipman, 1948; Ball, 1950) for the demonstration of the rheumatoid factor in the present series, and have found a negative correlation between levels of serum complement and this factor. This relationship was confirmed using a gel-precipitin method to demonstrate the rheumatoid factor and is evidence that serum complement levels become less elevated as the rheumatoid activity progresses and as the rheumatoid factor concentration in the serum is increasing.

It is known that the rheumatoid factor is an S19 gamma globulin and that, whilst it has some of the physico-chemical and immunological features of S19 antibodies, other properties resemble those of complement. It is not, however, one of the known components of the complement–properdin system (Edelman, Kunkel, and Franklin, 1958). In the present study the negative correlation between complement and rheumatoid factor is further evidence that they are distinct.

It has been shown that antibody which flocculates rapidly fixes complement (Hill and Osler, 1955) and, although we have observed that complement is not essential for the interaction of rheumatoid factor and aggregated gamma globulin, it is possible that it may still be precipitated in the presence of the insoluble antigen-antibody complex. This may explain the return of complement levels towards normal during the course of rheumatoid disease, when the rheumatoid factor is increasing.

Summary

Serum complement estimations have been performed in 106 patients suffering from rheumatoid disease (78 cases), systemic lupus erythematosus (18 cases), and several miscellaneous disorders—dermatomyositis, scleroderma, and polyarteritis nodosa (10 cases).

In rheumatoid disease, although many cases have raised serum complement levels, a number have values within the normal range. The mean for all cases of rheumatoid disease is significantly raised compared with the mean for 143 control subjects. There is a negative correlation between serum complement levels and those of rheumatoid factor estimated by sensitized sheep-cell agglutination or by a precipitin technique. A single case of rheumatoid disease in which the serum complement level was low is attributed to the presence of anticomplementary substances in the serum.

In active untreated systemic lupus erythematosus, serum complement is depressed and this is considered to be a true reduction in concentration not fully accounted for by the presence of anticomplementary substances. This concept is supported by the application of a new gel-diffusion precipitin technique for the estimation of a component of complement.

The elevation of serum complement in rheumatoid disease is thought to be a non-specific reaction to the inflammatory process, whereas the depression in lupus erythematosus is consistent with an underlying immune mechanism involving *in vivo* complement-fixing antigen-antibody reactions.

We wish to acknowledge with gratitude the co-operation of Dr. C. F. Hawkins and other physicians of the United Birmingham Hospitals. We are indebted to Professor J. R. Squire for his criticism and advice, to Dr. J. F. Soothill for collaborating with the gel-diffusion precipitin technique, and to Misses M. Phillips and A. Hudson for their valuable technical assistance. One of us (H.A.E.) was in receipt of a research grant from the United Birmingham Hospital Endowment Fund during the time this study was undertaken. The work was supported in part by a grant from the Empire Rheumatism Council.

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Complément sérique, facteur rhumatismal et autres protéines sériques dans la maladie rhumatismale et le lupus érythémateux disséminé

RÉSUMÉ

Le complément sérique fut dosé chez 106 malades, dont 78 atteints de maladie rhumatismale, 18 de lupus érythémateux disséminé et 10 souffrant de troubles divers, tels que dermatomyosite, sclérodermie et polyartérite noueuse.

Dans la maladie rhumatismale, bien que beaucoup de cas ont un titre du complément sérique élevé, d'autres ont un titre normal. La moyenne pour tous les cas de maladie rhumatismale est appréciablement élevée, en comparaison à la moyenne chez 143 témoins. Il y a une corrélation négative entre les titres du complément sérique et ceux du facteur rhumatismal déterminé par l'agglutination des globules sensibilisées de mouton ou par le procédé de précipitine. Un seul cas de maladie rhumatismale, où le titre du complément sérique était bas, est attribué à la présence de substances anticomplémentaires dans le sérum.

Dans le lupus érythémateux disséminé non-traité, le complément sérique est bas et on croit qu'il s'agisse ici d'une vraie réduction du taux que l'on ne peut pas expliquer entièrement par la présence de substances anticomplémentaires. Cette théorie est supportée par l'application d'un nouveau procédé de *gel-diffusion precipitin* pour déterminer un composé d'un complément.

On pense que l'élévation du complément sérique dans la maladie rhumatismale est une réaction non-spécifique du processus inflammatoire, tandis que sa diminution dans le lupus érythémateux s'explique par un mécanisme immunologique profond, lié *in vivo* aux réactions entre l'antigène et l'anticorps fixant le complément.

Complemento sérico, factor reumatoide y otras proteinas séricas en la enfermedad reumatoide y en el lupus eritematoso diseminado

SUMARIO

Se determinó el complemento sérico en 106 enfermos, de los cuales 78 con enfermedad reumatoide, 18 con lupus eritematoso diseminado y 10 con varios disturbios, como dermatomiositis, esclerodermia y poliarteritis nodosa.

En la enfermedad reumatoide, aunque en muchos casos las cifras del complemento sérico se ven aumentadas, en otros éstas se encuentran dentro de los límites normales. El promedio para todos los casos de enfermedad reumatoide está significativamente alzado, en comparación con el promedio en 143 testigos. Hay correlación negativa entre las tasas del complemento sérico y las del factor reumático determinado por la aglutinación de globulos sensibilizados de oveja o por el procedimiento de precipitina. Un solo caso de enfermedad reumatoide, en el cual la tasa del complemento sérico fué baja, se atribuye a la presencia de substancias anticomplementarias en el suero.

En el lupus eritematoso diseminado sin tratar, el complemento sérico está bajo; se cree que se trataría aquí de una reducción verdadera de la concentración, que no se puede explicar enteramente por la presencia de substancias anticomplementarias. Este concepto se ve apoyado por los resultados de un nuevo procedimiento de *gel-diffusion precipitin* para determinar un compuesto de un complemento.

Se cree que el aumento del complemento sérico en la enfermedad reumatoide constituye una reacción nonespecífica del proceso inflamatorio, mientras que su baja en el lupus eritematoso se explica por un mecanismo imunológico profundo, ligado *in vivo* a reacciones entre al antígeno y el anticuerpo resultando en la fijación del complemento.

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DIFFERENTIAL AGGLUTINATION TITRE (D.A.T.) IN JUVENILE RHEUMATOID ARTHRITIS

BY

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This study concerns the titre of differential sheep cell agglutination (Rose-Waaler) in rheumatoid arthritis affecting children, its variability and its correlation with other clinical features, during a period of at least 4 years' observation.

Method

The technique employed from 1949-1956, which has been described by one of us (Scott, 1952), was a slight modification of the method originally proposed by Rose, Ragan, Pearce, and Lipman (1948). Since 1956, a further modification has been employed, as suggested by Greenbury (1957), using Perspex trays (M.R.C. pattern) in place of tubes and racks. This method will be described in detail elsewhere (Bywaters and Scott, unpublished). The results by the two methods are closely comparable, the newer method giving more consistent results.

The results are expressed as a differential titre (ratio) in both methods, and the lowest ratio accepted as positive in a series of doubling dilutions is 1 : 16. Slight changes in the sensitivity of the method have been found to occur because of variations in agglutinability of red cell suspensions from different sheep, amounting usually to not more than a one-tube difference. A single positive result occurring in the midst of a series of negative tests in one individual is therefore suspect and may well be due to technical factors, although in an attempt to control this, sera of known titre were included as a safeguard in each series of titrations.

Material

This series consists of 142 patients (85 females and 57 males) admitted to this Unit from its inception in 1947 to the end of 1953, and followed to December 31, 1957, giving, for the purpose of this study, a maximum follow-up period of 10 years and a minimum of 4 years; since the D.A.T. test was not started here until January, 1949, the period of D.A.T. observation ranges from 4 to 8 years in all cases, except in two patients who died and were followed for 3 years only. The 142 cases were all under 16 years of age at the onset of their illness.

75 patients were first seen more than one year after the onset of disease (referred to as "late" cases) and 67 within one year of onset ("early" cases). Patients were seen after discharge as a rule at least yearly when blood was taken. The mean number of D.A.T.s done per patient in this study was 9·5 (ranging from 2 to 24).

The diagnostic criteria for admission to the series were as follows:

(*i*) Polyarthritis affecting four or more joints, past or present, other diagnoses having been excluded.

(*ii*) Less than four joints involved, but diagnosis confirmed by synovial biopsy. Four patients had three joints involved, six had two joints involved, and three had one joint involved. Twelve of these thirteen patients had biopsy confirmation; the thirteenth was a child with monarthritis who also had iritis and had been followed for 8 years.

These criteria included five patients with psoriasis, (four with negative D.A.T.s and one with one D.A.T. at 1 : 32), one patient with ulcerative colitis, and one with sacro-iliac involvement.

Disease activity was considered to be present if there was active joint involvement with two out of the four following:

(1) Joint pain.
(2) Joint warmth.
(3) Joint limitation of movement.
(4) Joint swelling.

Results

Table I shows the results taking all D.A.T.s done (Groups I-III) and Table II the results of only the first D.A.T. done (Groups IV and V). The distribution of sex within these groups and the mean duration of follow-up are also shown. The difference between the mean duration of follow-up of Group I "all negative" (5·2 yrs) and of Group III "two or more positive" (6·1 yrs) is statistically significant ($p = <0{\cdot}01$), but this does not affect the conclusions drawn from subsequent Tables. The only possible inference is that a slightly greater number of patients might become sero-positive if followed for longer periods.

The intermediate Group II of 36 patients with only one positive D.A.T. (Table I) we have found to resemble more closely the negative group as regards age and sex incidence (see Tables III and IV), whether the lone positive result was 1 : 16 (21 cases) or 1 : 32 or more (15 cases); 32 out of the 36 had between six and 21 estimations made, the remaining four having two, three, four, and four respectively. Altogether, in these 36 patients, the single positive result represented in most cases under 20 per cent. of all D.A.T.s done, whereas in the 28 cases with more than one positive result, the positive results represent 60 per cent. of all D.A.T.s done. We feel that some of these single positive results in the midst of a negative series might possibly be due to technical error.

Age Incidence.—Table III (opposite) shows that the proportion of cases in which the first D.A.T. was positive increased markedly with age at onset. A similar relationship to age at onset is seen in the positive cases (Group III), but not in the negative cases (Group I) or in the doubtful positive cases (Group II), although the difference between the positive and

TABLE I

RESULTS OF ALL TESTS DONE IN 142 CASES, BY SEX, MEAN DURATION OF FOLLOW-UP, AND MEAN DURATION FROM ONSET TO TIME FIRST EXAMINED

Group	D.A.T. Results	Cases		Sex		First Examined		Mean Duration of Follow-up (yrs)	Mean Duration of Disease before First Examination (yrs)
		No.	Per cent.	Male	Female	"Late" >1 yr from Onset	"Early" <1 yr from Onset		
I	All Negative	78	54·9	28	50	38	40	*5·2 {5·3 (M) 5·1 (F)}	2·4
II	One Positive Only	36	25·4	12	24	18	18	5·9 {5·8 (M) 5·9 (F)}	2·3
III	Two or More Positive	28	19·7	17	11	19	9	*6·1 {6·3 (M) 5·7 (F)}	2·3
Total		142	—	57	85	75	67	5·7	2·3

* Difference between these two means = 0·9
Standard error of this difference = 0·27
$\therefore c = 0{\cdot}9/0{\cdot}27 = 3{\cdot}33$ ($p = <0{\cdot}01$)

TABLE II

RESULTS OF FIRST D.A.T. IN 142 CASES, BY SEX, MEAN DURATION OF FOLLOW-UP, AND MEAN DURATION FROM ONSET TO TIME FIRST EXAMINED

Group	First D.A.T. Results	Cases		Sex		First Examined		Mean Duration of Follow-up (yrs)	Mean Duration of Disease before First Examination (yrs)
		No.	Per cent.	Male	Female	"Late" >1 yr from Onset	"Early" <1 yr from Onset		
IV	Positive	19	13·4	11	8	11	8	5·9 {5·7 (M) 6·1 (F)}	2·2
V	Negative	123	86·6	46	77	64	59	5·5 {5·6 (M) 5·4 (F)}	2·4
Total		142	—	57	85	75	67	5·7	2·3

TABLE III

AGE INCIDENCE

Group	IV	I	II	III
Age at Onset (yrs)	Total No. of Cases	First D.A.T. Positive	D.A.T.s All Negative	Only One Positive D.A.T.	Two or More Positive D.A T.s
1–4	43	1 (2%)	29 (67·4%)	10 (23·3%)	4 (9·3%)
5–9	43	6 (14%)	20 (46·4%)	14 (32·6%)	9 (21%)
10–16	56	12 (21·5%)	29 (51·6%)	12 (21·4%)	15 (27%)
	142	19 (13·4%)	78 (54·9%)	36 (25·4%)	28 (19·7%)
Mean Duration of Follow-up (yrs)		5·9	5·2	5·9	6·1

negative groups is just not significant ($0{\cdot}1 > p > 0{\cdot}05$) at the 5 per cent. level. Table III also shows the mean duration of follow-up for each of the groups. The positive cases (Group III) were followed slightly longer than the all-negative cases (Group I), which may have exposed them to a slightly greater risk of giving a positive result, but this would not have influenced those whose first D.A.T. was positive (Group IV), who were followed as long as the more highly-positive group and who also showed a tendency for more positive results in the older age groups.

Table IIIA shows the mean duration of follow-up for each of the three age groups, 1-4, 5-9, and 10-16 yrs, and the mean duration of disease from onset. The oldest group, which was most frequently positive, was followed for a slightly shorter period than the younger groups, so that the significance of the trend for positives to occur in the older group is not altered by length of follow-up, nor by the duration of disease.

TABLE IIIA

AGE INCIDENCE AND MEAN DURATION OF DISEASE AND LENGTH OF FOLLOW-UP IN THREE GROUPS

Age at Onset (yrs)	Total No. of Cases	Mean Duration of Follow-up (yrs)	Mean Duration of Disease from Onset to End of Follow-up (yrs)
1–4	43	5·5	9·2
5–9	43	5·8	7·7
10–16	56	5·3	6·7

Sex Incidence.—In Table IV the observed numbers of positive and negative cases in each of the various groups have been compared with the expected numbers on the nul hypothesis, and the χ^2 values calculated.

The proportion of males to females is the same in Groups I and II, but in Groups IV and III males are more frequently D.A.T.-positive than females, although this only approaches statistical significance in Group III (χ^2, Yates' modification = 3·36; $0{\cdot}1 > p > 0{\cdot}05$). Although the males were followed for 5·8 years (mean) and the females for 5·5 years (mean), this does not alter the conclusions stated above, as in Group III both sexes fell into the longest follow-up period (mean 6·1 yrs).

TABLE IV

SEX INCIDENCE

Group	IV	I	II	III
Sex	Total No. of Cases	First D.A.T. Positive	D A.T.s All Negative	Only One D.A.T. Positive	Two or More D.A.T.s Positive
Male	57	11	28	13	16
Female	85	8	50	23	12
Total	142	19	78	36	28
		NS $\chi^2 = 2{\cdot}08$	NS $\chi^2 = 0{\cdot}93$	NS $\chi^2 = 0{\cdot}14$	NS $\chi^2 = 3{\cdot}36$

Variation of D.A.T. during Course of Disease.—This has been examined for each 2-year period of observation, in respect both of tests (Table V) and of persons (Table VI), in the group of 64 children with at least one positive D.A.T. during observation. Tables VA and VIA show the total series of 142 cases.

These four Tables show a tendency for the D.A.T. to become negative with duration of disease. This tendency was slightly more marked in the early cases. In both early and late cases some initially positive changed to negative and *vice versa*. Only nine of the 64 patients showed at least one positive result each year.

TABLE V
PROPORTION OF POSITIVE D.A.T.s TO TOTAL NUMBER DONE IN 2-YEAR PERIODS ON 64 PATIENTS WITH AT LEAST ONE POSITIVE D.A.T. DURING OBSERVATION

First Examined	No. of Cases	Years of Observation								Total D.A.T.s Done on 64 Patients
		1st and 2nd		3rd and 4th		5th and 6th		7th and 8th		
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	
Early ..	27	38/175	21·7	13/78	16·7	5/44	11·4	1/21	4·8	318
Late ..	37	60/185	32·4	32/105	30·5	22/86	25·6	6/40	15	416
Total ..	64	98/360	27·2	45/183	24·6	27/130	20·8	7/61	11·5	734

TABLE VA
PROPORTION OF POSITIVE D.A.T.s TO TOTAL NUMBER DONE IN 2-YEAR PERIODS IN THE TOTAL SERIES OF 142 PATIENTS

First Examined	No. of Cases	Years of Observation								Total D.A.T.s Done on 142 Patients
		1st and 2nd		3rd and 4th		5th and 6th		7th and 8th		
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	
Early ..	67	38/325	11·7	13/157	8·3	5/103	4·8	1/39	2·6	638
Late ..	75	60/336	17·9	32/207	15·5	22/129	17·0	6/52	11·5	711
Total ..	142	98/611	16·0	45/364	12·4	27/232	11·6	7/92	7·6	1,349

TABLE VI
PROPORTION OF PATIENTS WITH A POSITIVE D.A.T. IN EACH 2-YEAR PERIOD TO NUMBER OF PATIENTS TESTED AT LEAST ONCE IN EACH 2-YEAR PERIOD

First Examined	No. of Cases	Years of Observation							
		1st and 2nd		3rd and 4th		5th and 6th		7th and 8th	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Early ..	27	20/27	74·1	7/25	28	5/21	23·8	1/9	11·1
Late ..	37	19/37	51·2	20/34	58·8	15/29	51·7	5/19	26·3
Total ..	64	39/64	61	27/59	45	20/50	40	6/28	21·5

TABLE VIA
PROPORTION OF PATIENTS WITH A POSITIVE D.A.T. IN EACH 2-YEAR PERIOD TO TOTAL NUMBER OF PATIENTS TESTED IN SERIES (142 CASES)

First Examined	No. of Cases	Years of Observation							
		1st and 2nd		3rd and 4th		5th and 6th		7th and 8th	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Early ..	67	20/66	32	7/56	12·5	5/48	10·4	1/17	5·8
Late ..	75	19/75	25·2	20/64	31·2	15/50	30	5/26	19·3
Total ..	142	39/141	27·6	27/120	22·3	20/98	22	6/43	14

Correlation of D.A.T. with Disease Activity.—Table VII compares disease activity and changes in D.A.T. during the observation period in three groups: Group I "negative", Group II "doubtful", and Group III "more positive". Each group is subdivided into early and late cases, but this subdivision shows little relevance.

The same proportion of sero-positive and sero-negative patients show activity which subsides, but a higher proportion of sero-positive patients remain active throughout their period of observation. None of the patients with a positive D.A.T. at some time were inactive throughout the observation period. Since those remaining active were followed for a slightly shorter period (mean 5·3 yrs) than those who became inactive (mean 5·7 yrs), it is reasonable to expect that the former group would eventually become inactive given more time.

Of the 64 patients who had a positive D.A.T. at some time, 35 had negative results in the first year and became positive later; 29 were positive at some time in the first year of observation and became negative later. Of the 35 cases in which the D.A.T.s were at first negative and later became positive, eleven were seen within the first year of their illness ("early") and information on the duration of "negativity" is therefore available. This averaged nearly 4 years (Table VIII) with a range from 2 to 7 years, nearly equal numbers changing over in each of the three age groups (0-9, 10-16, and 17-20). Ten out of eleven patients had active disease when the first D.A.T. (negative) was done and five out of eleven patients had active disease when the D.A.T. became positive.

The D.A.T. became negative between 0 and 8 years of age in three cases, between 9 and 16 years in eight cases, and between 17 and 20 years in three cases. All fourteen patients had active disease when the first D.A.T. (positive) was done and five of them still had active disease when the D.A.T. became negative. The mean duration of "positivity" in these fourteen cases was 2·3 years.

Table VIII and Table IX (overleaf) show that as many patients became negative as became positive in the older groups. These Tables also show that there is no strict correlation between D.A.T. "positivity" and disease activity. When the D.A.T. is negative, this is not unexpected, since a large number of patients had negative D.A.T.s throughout, despite disease activity at some time in 69 out of 78 cases.

TABLE VII
CORRELATION OF D.A.T. WITH DISEASE ACTIVITY

Group	No. of Cases	Results of D.A.T. during Observation	First Examined	Disease Activity							
				Inactive Becoming Active		Inactive Throughout		Active Becoming Inactive		Active Throughout	
				No.	Percent.	No.	Percent.	No.	Percent.	No.	Percent.
I	78	Negative	Early .. 3 Late .. 3 } 6	7·7	6 3 } 9	11·5	29 19 } 48	61·5	1 14 } 15	19·2
II	36	Only One Positive	Early .. 1 Late .. 1 } 2	6	0		14 13 } 27	75	3 4 } 7	19
III	28	Two or More Positive	Early .. 0 Late .. 1 } 1	3·6	0		7 8 } 15	53·6	2 10 } 12	42·8
Total ..	142	—	—	9	—	9	—	90	—	34	—

TABLE VIII
DURATION OF NEGATIVE RESPONSE IN ELEVEN "EARLY" CASES WHO CONVERTED TO POSITIVE LATER

Age at Onset when D.A.T. was Negative (yrs)	Disease Activity when First Examined	Age when D.A.T. First Positive (yrs)	Disease Activity when D.A.T. First Positive	Time Interval before D.A.T. Positive for First Time (yrs)
1	−	3	+	2
5	+	7	−	2
5	+	9	+	4
5	+	7	−	2
5	+	12	+	7
6	+	8	−	2
8	+	11	−	3
9	+	12	−	3
12	+	18	−	6
14	+	20	+	6
15	+	19	+	4
11	−	−	−	Mean 3·7

TABLE IX

DURATION OF POSITIVE RESPONSE IN FOURTEEN "EARLY" CASES WHO CONVERTED TO NEGATIVE LATER

Age at Onset when D.A.T. was Positive (yrs)	Disease Activity when First Examined	Age when D.A.T. was First Negative (yrs)	Disease Activity when D.A.T. was First Negative	Time Interval before D.A.T. Negative for First Time (yrs)
1	+	3	−	2
2	+	5	−	3
6	+	8	−	2
7	+	9	−	2
9	+	11	+	2
10	+	12	−	2
11	+	15	−	4
12	+	15	+	3
12	+	14	+	2
13	+	15	+	2
14	+	16	+	2
15	+	17	−	2
15	+	18	−	3
15	+	17	−	2
14				Mean 2·3

Note: The remaining two "Early" cases out of the total 27 "Early" cases who had a positive D.A.T. at some time did not convert from positive to negative during their period of observation.

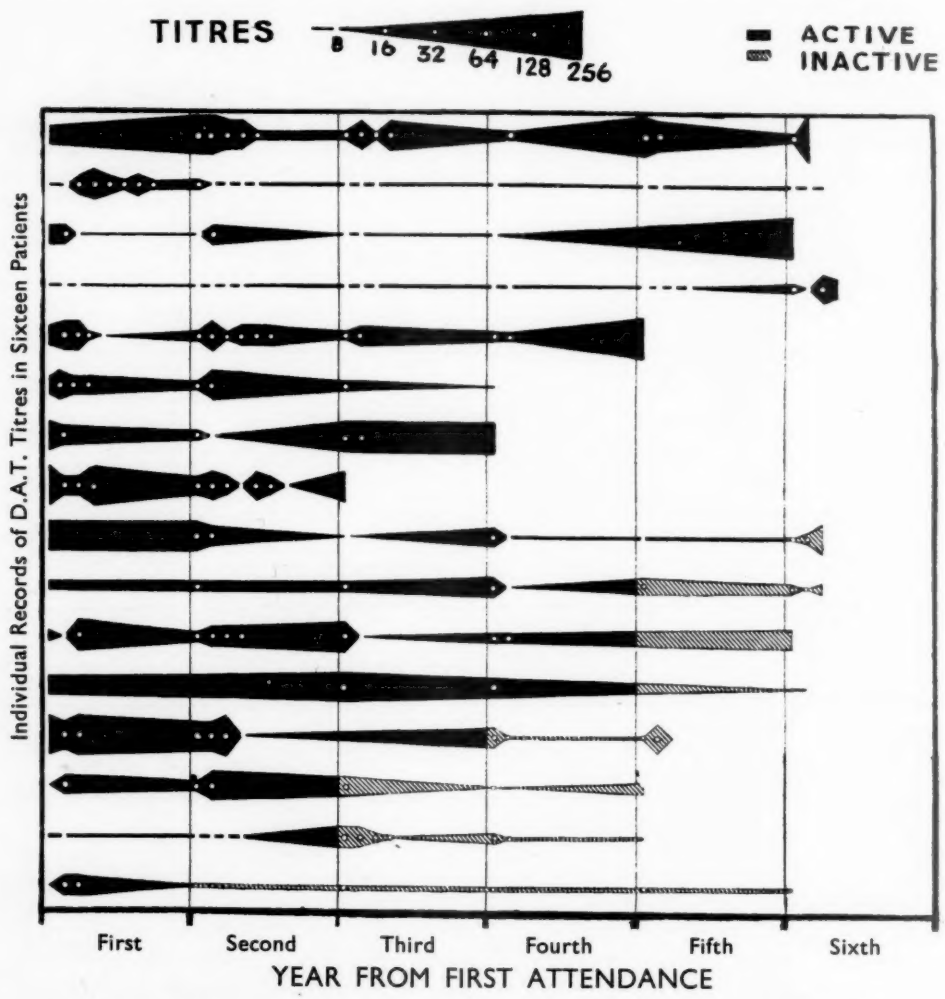

Figure.—Variation of titre in relation to disease activity in sixteen patients with Still's disease.

The Figure shows the pattern of D.A.T. response in the sixteen patients who had two or more positive D.A.T.s at 1 : 32 or more. These patterns show that there is no particular trend in the behaviour of D.A.T. titres for individuals, and no two cases showed any similarity of pattern; this supports the statement made above that there is no strict correlation between D.A.T. positivity and disease activity. (The white dots in the Figure indicate the sequence of tests done, but are not related to the date when they were performed in each year.)

Although, as shown in Table III, serological positivity is more frequent in children whose disease starts in their 'teens, there seems to be little tendency for the group of children who are younger at the time of onset to convert to sero-positivity when they reach their 'teens. However, our period of observation is short and our numbers few. This is an important point which will be decided by further observation.

We have also tried to correlate the D.A.T. in these children with other clinical features, such as rash, nodules, erosions, lymphadenopathy, and splenomegaly (Table X). Although splenomegaly was found more commonly in the positive groups to a significant degree ($0{\cdot}05 > p > 0{\cdot}02$), many comparisons are being made using the same data and a higher level of significance is needed.

If, however, we select the 28 highly positive cases (Group III: two or more positive D.A.T.s during observation) for comparison with the rest (Table XI), a greater probability emerges that nodules are related to D.A.T. positivity ($p = > 0{\cdot}001$), as is known to be the case in adult rheumatoid arthritis (Ball, 1952).

Summary

142 patients suffering from Still's disease were followed for from 4 to 8 years; 13·4 per cent. had a positive D.A.T. (1 : 16 or more) at the first test, and 19·7 per cent. had two or more positive D.A.T.s. The mean number of D.A.T.s performed on each patient was 9·5.

Sero-positivity was more frequent in those patients who were older at the time of onset, but there was little tendency for those who were younger at onset to convert to sero-positivity when they reached their 'teens. Males tended to be more frequently sero-positive than females.

TABLE X

CORRELATION OF D.A.T. WITH OTHER CLINICAL FEATURES

Group	D.A.T. Results	Total No. of Cases	Clinical Features									
			Rash		Nodules		Splenomegaly		Lymphadeno-pathy		Erosions	
			No.	Percent.	No.	Percent.	No.	Percent.	No.	Percent.	No.	Percent.
III	Two or More Positive	28	6	22	7	25	8	29	18	64	14	50
II	One Only Positive	36	10	28	0	0	13	36	14	39	12	33
I	All Negative ..	78	21	27	4	5	13	17	35	45	22	56
Total		142	37	—	11	—	34	—	77	—	48	—

TABLE XI

CORRELATION OF D.A.T. WITH OTHER CLINICAL FEATURES

Group	D.A.T. Results	Total No. of Cases	Clinical Features									
			Rash		Nodules		Splenomegaly		Lymphadeno-pathy		Erosions	
			No.	Percent.	No.	Percent.	No.	Percent.	No.	Percent.	No.	Percent.
III	Two or More Positive	28	6	21·8	7	25	8	28·6	18	64·2	14	50
I and II	All Negative or Only One Positive	114	31	27·2	4	3·5	26	22·8	49	42·9	34	29·8
Total		142	37	—	11	—	34	—	77	—	48	—
			$\chi^2 = 0{\cdot}15$ NS		$\chi^2 = 11{\cdot}6$ $P = <0{\cdot}001$		$\chi^2 = 0{\cdot}1$ NS		$\chi^2 = 3{\cdot}2$ $P = 0{\cdot}1$–$0{\cdot}05$		$\chi^2 = 3{\cdot}2$ $P = 0{\cdot}1$–$0{\cdot}05$	

There was no typical pattern of D.A.T. response throughout the period of follow-up; there was no correlation with duration of disease and little correlation with disease activity.

An attempt was made to correlate the D.A.T. with other clinical features, such as rash, nodules, erosions, lymphadenopathy, and splenomegaly. When the highly-positive group (two or more positive D.A.T.s) was compared with the remainder, nodules appeared to be related to sero-positivity, as in adult patients.

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Titre d'agglutination différentielle (D.A.T.) dans l'arthrite rhumatismale juvénile

RÉSUMÉ

On observa 142 cas de maladie de Still pendant 4 à 8 ans; 13,4% de ces cas accusèrent un D.A.T. positif (1 : 16 ou plus) à la première détermination et 19,7% eurent deux ou plus titres positifs. En moyenne, le D.A.T. fut effectué 9,5 fois chez chaque malade.

La séro-positivité fut plus fréquente chez des enfants plus âgés au moment du début de la maladie, mais il n'y eut qu'une tendance faible chez des enfants à début précoce à devenir séro-positifs après avoir dépassé l'âge de 10 ans. Les garçons tendaient à être séro-positifs plus souvent que les filles.

Pendant toute la période d'observation on ne vit aucun tableau typique de D.T.A.; il n'y eut pas de corrélation avec la durée de la maladie et peu de corrélation avec son évolution.

On essaya de mettre en corrélation le D.A.T. et les autres caractères cliniques, tels que nodules, exanthème, érosions, lymphadenopathie et splénomégalie. En comparant le groupe fortement positif (deux ou plus D.A.T. positifs) avec le reste, on trouva, comme chez des adultes, une plus grande fréquence des nodules dans ce groupe.

Cifra de aglutinación diferencial (D.A.T.) en la artritis reumatoide juvenil

SUMARIO

Se observaron 142 casos de enfermedad de Still durante 4 a 8 años; en un 13.4% ellos la réaction de aglutinación diferencial fué positiva (1 : 16 o más) en la primera determinación y en un 19,7% se obtuvo dos o más reacciones positivas. En promedio se procedió a 9,5 determinaciones de la D.A.T. en cada enfermo.

La sero-positividad fué más frecuente en niños de mayor edad al tiempo del comienzo de la enfermedad, pero niños enfermos desde la edad más tierna tuvieron poca tendencia a convertirse en sero-positivos después de rebasar la edad de 10 años. Los chicos tendían a presentar reacciones sero-positivas más frecuentemente que las chicas.

Durante el entero período de observación no se dibujó ningún cuadro típico de la D.A.T.; tampoco se observó correlación alguna con la duración de la enfermedad, ni mucha con su evolución.

Se tentó correlacionar la D.A.T. con otros rasgos clínicos, como exantema, nódulos, erosiones, linfadenopatía y esplenomegalía. Al comparar el grupo fuertemente positivo (dos o más D.A.T. positivas) con los demás, se vió, como en enfermos adultos, una relación entre nódulos y sero-positividad.

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COMPARISON OF DIFFERENTIAL AGGLUTINATION TITRE (D.A.T.) IN JUVENILE AND ADULT RHEUMATOID ARTHRITIS

BY

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In the preceding paper (Bywaters, Carter, and Scott, 1959), it was shown that the Rose-Waaler test (positive in about 50 to 70 per cent. of adult rheumatoid arthritis cases) is frequently negative in childhood arthritis (Still's disease). This has also been remarked by others (Pike, Sulkin, and Coggeshall, 1955; Alexander and de Forest, 1954; Ziff, 1957), although by the inhibition technique 95·8 per cent. are positive (McEwen, Ziff, Carmel, Di Tata, and Tanner, 1958).

This raises the possibility that Still's disease is different from the rheumatoid arthritis seen typically in adults, as Still (1897) originally postulated. To provide further data pertinent to this, we have estimated the Rose-Waaler titre over a period of several years in a series of over 200 children and this report compares the titre in 142 juvenile cases followed for a minimum of 4 years with an adult group of rheumatoid arthritis patients. All sera were tested by one of us (F.E.T.S.) by the method described in the previous paper (Bywaters and others, 1959).

Material

The juvenile series of 142 patients is defined in the preceding paper. The adult series consists of 140 patients followed for at least 4 years, ninety from Hammersmith Hospital and fifty from Taplow, who fulfil the same criteria as those used for the juvenile group; four patients had less than four joints involved; three had three joints involved, and one had one joint only involved, but diagnosis was confirmed by synovial biopsy in these four cases.

The adults are thus comparable with the juvenile series except that single or infrequent Rose tests were performed. This difference is of no importance in analysing all tests according to decade (Figs 1 and 2), but would affect a comparison of patients according to decade, taking the Taplow juvenile and adult group together by decade at onset. For this reason, in tabulations subsequent to Figs 1 and 2, only the result of the first D.A.T. is taken into account.

However, for the purpose of comparing the D.A.T. titres at various decades, we could not include the ninety Hammersmith adults reported as positive or negative only, and there were thus too few adults in some of the decade groups. Thus, for Figs 1 and 2, 21 adults from Taplow were added (making a total of 71 adults and 142 children). These 21 patients were similar to the larger group of fifty Taplow adults except that they had not been followed for 4 years. They could not therefore be used for correlation of clinical phenomena shown over a 4-year period with the first D.A.T., which is the subject of Tables III and IV, and Figs 3, 4, and 5.

The functional state of the patient is graded from I to V:

Grade	I	Helpless
	II	Chair/bed existence
	III	Moderate limitation of function
	IV	Slight limitation of function
	V	No limitation of function

Results

Table I (overleaf) compares the juvenile and adult cases in regard to sex, interval between onset and admission to hospital, and result of first Rose-Waaler test. Females preponderate in the adult series and juvenile rheumatoid arthritis is less frequently sero-positive.

Fig. 1 (overleaf) shows a progressive increase in positive D.A.T. results with lateness of onset, whatever definition of "positivity" is adopted. The most valid curve is the dotted line which shows only the result of the first test performed.

TABLE I

COMPARISON OF JUVENILE AND ADULT SERIES, BY SEX, DURATION OF DISEASE FROM ONSET, AND RESULT OF FIRST D.A.T.

Total No. of Patients		Sex		First Examined		Patients with D.A.T. Positive at First Test	
		Male	Female	"Late" >1 yr from Onset	"Early" <1 yr from Onset	No.	Per cent
Adult ..	140	37	103	71	69	70	50
Juvenile ..	142	57	85	75	67	19	13·4

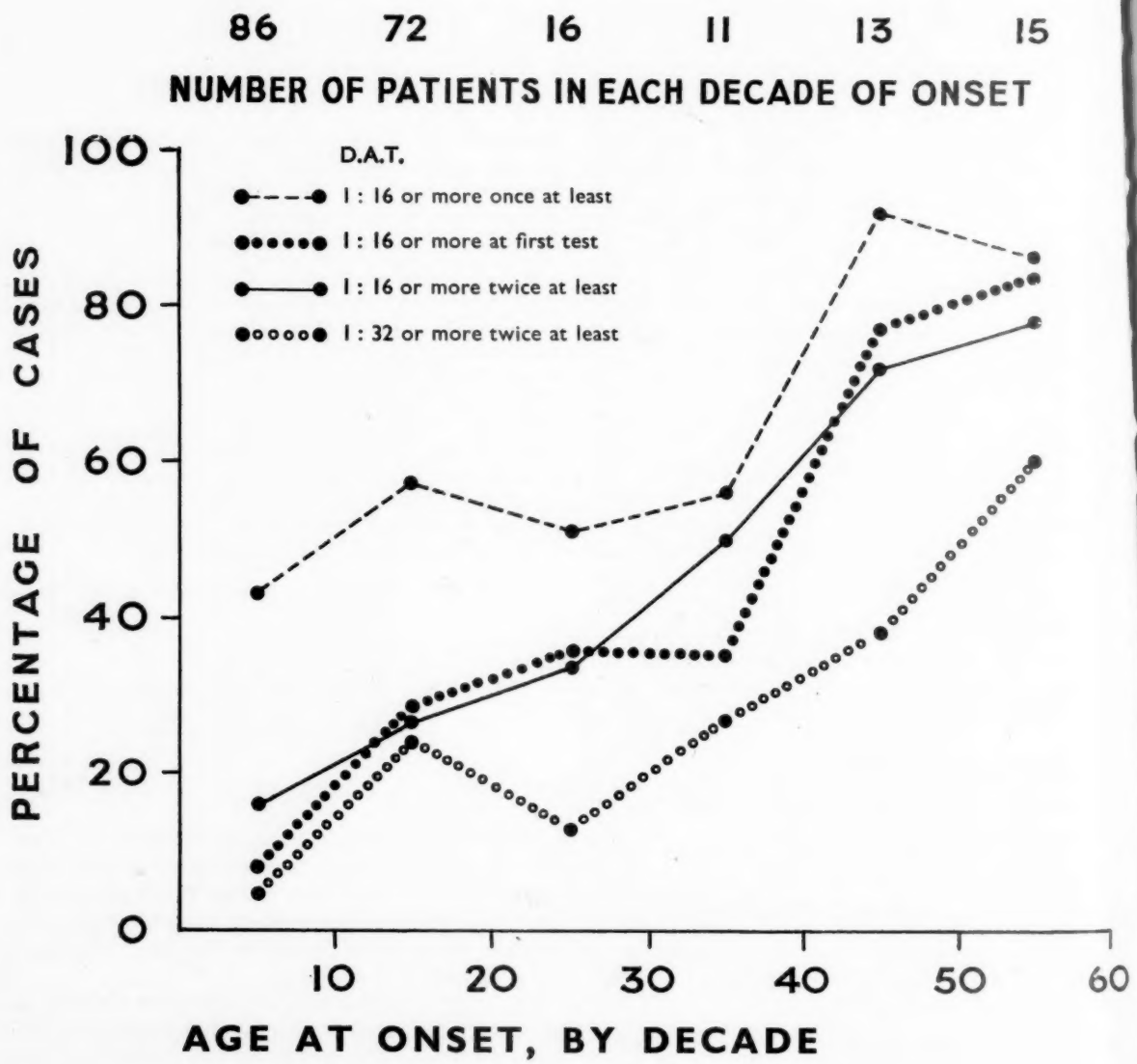

Fig. 1.—Correlation of D.A.T. results with age at onset, taking four levels of "positivity".

Fig. 2 shows the percentage distribution by titre of all estimations done on patients in each decade.

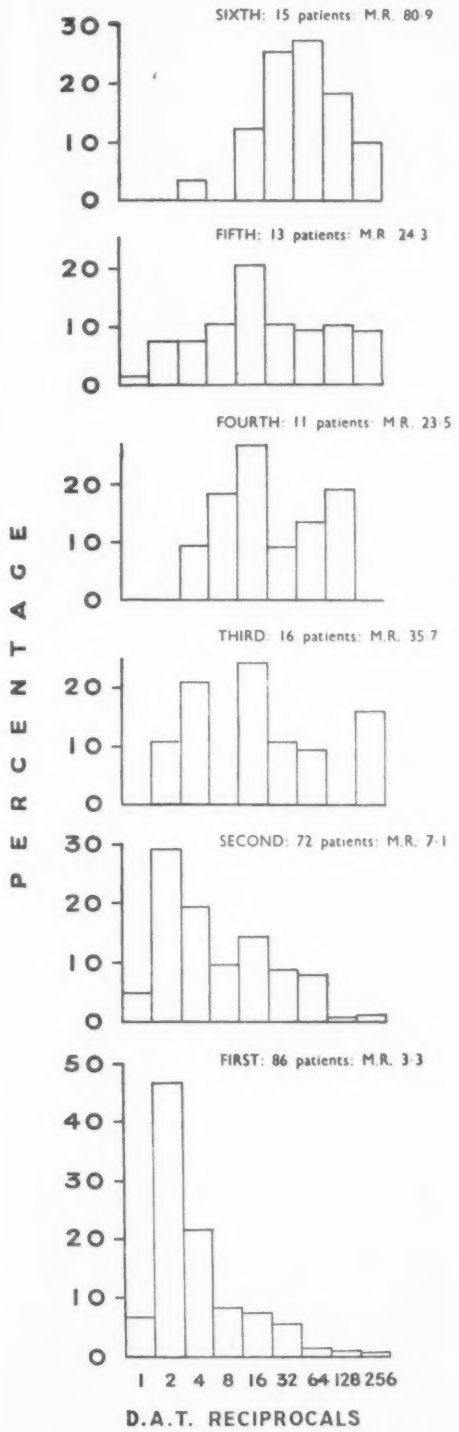
SIXTH: 15 patients: M.R. 80·9
FIFTH: 13 patients: M.R. 24·3
FOURTH: 11 patients: M.R. 23·5
THIRD: 16 patients: M.R. 35·7
SECOND: 72 patients: M.R. 7·1
FIRST: 86 patients: M.R. 3·3
PERCENTAGE
1 2 4 8 16 32 64 128 256
D.A.T. RECIPROCALS

Fig. 2.—Percentage distribution of titre in each of six decades. (M.R. = mean reciprocal).

It will be seen that there is a progressive increase in the frequency of high titres with age. The reciprocal of the mean (logarithmic) titre at each decade ("M.R." on the graph) also shows a progressive rise apart from two points. The number of patients in each decade is the same as in Fig. 1.

The numbers of patients in each decade and the D.A.T. results given in Table II apply to all the subsequent Figures and Tables.

TABLE II

DISTRIBUTION OF 282 PATIENTS IN DECADES AND OF FIRST POSITIVE D.A.T.s

Decades . .	0-9	10-19	20-29	30-39	40-49	50-59	60+
No. in Each Decade . .	86	71	20	30	28	32	15
First D.A.T. Positive (1:16 or More) . .	7	18	7	14	15	20	8

Since a rash is one of the more prominent features of the juvenile disease (Isdale and Bywaters, 1956) and nodules are more prominent in older patients (Bywaters, Glynn, and Zeldis, 1958), we have studied these two features, together with the improvement in functional state over the 4 years, as reflecting prognosis.

Fig. 3 (overleaf) shows the percentage of D.A.T. positive and D.A.T. negative patients in each decade, who showed a rash. The total percentage of patients with a rash in each decade is indicated by the dotted line. The incidence of rash falls rapidly with age, and there is no correlation with the D.A.T. response.

Fig. 4 (overleaf) similarly shows the percentage of all D.A.T. positive patients and of all D.A.T. negative patients in each decade who showed nodules. It will be seen that at each decade a higher proportion of the D.A.T. positive group than of the D.A.T. negative group had nodules. The total percentage of patients with nodules in each decade is indicated by the dotted line. The incidence of nodules increases with age.

Prognosis.—This appears better in the young, because almost 88 per cent. improved over the 4-year period as against 50 per cent. in adults. Tables III and IV (overleaf) show the details of improvement or deterioration of 136 "early" patients out of the total 282, divided into four age groups at onset, and also compares sero-positive (at least one positive D.A.T.) with sero-negative patients. The mean functional status when first seen and at the fourth follow-up is given for the various age groups.

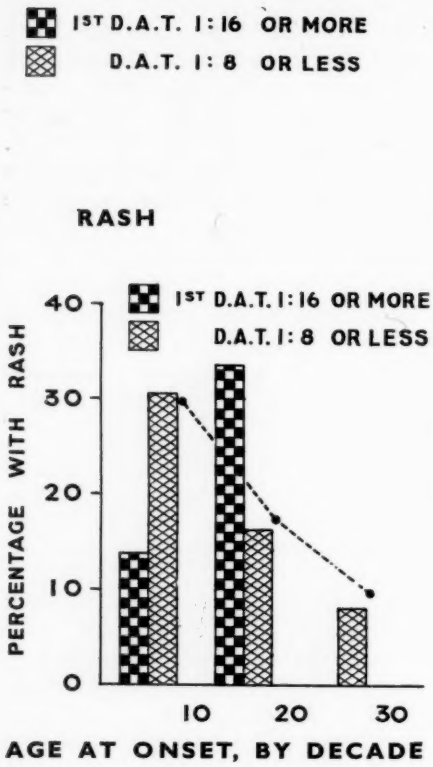

Fig. 3.—Correlation of rash with D.A.T. Percentage of patients in each decade with rash, according to D.A.T. titre, in a series of 282 cases. Dotted line indicates total percentage of patients with rash in each decade.

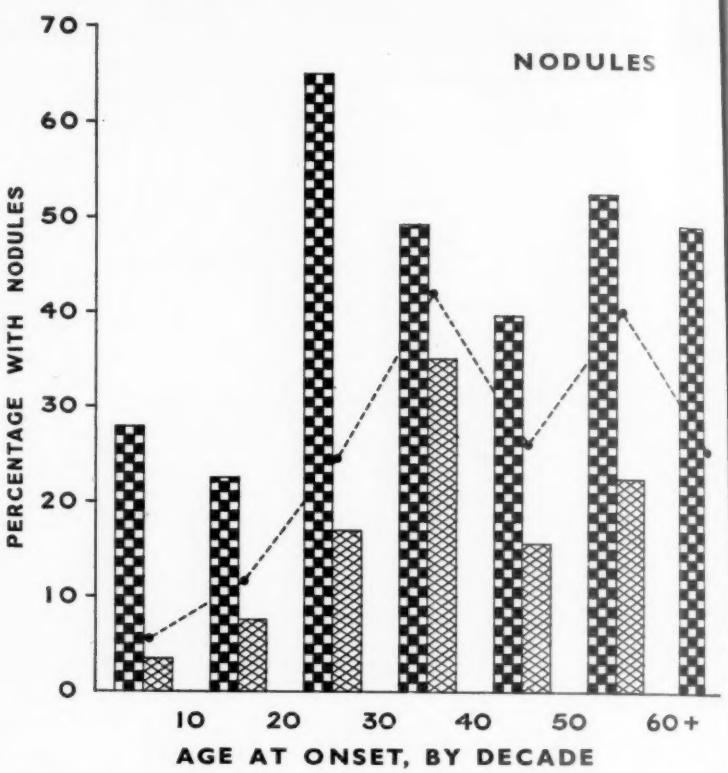

Fig. 4.—Correlation of nodules with D.A.T. Percentage of patients in each decade with nodules, according to D.A.T. titre, in a series of 282 cases. Dotted line indicates total percentage of patients with nodules in each decade.

TABLE III

CHANGE IN FUNCTIONAL STATUS AT FOLLOW-UP IN EARLY CASES (CHILDREN AND ADULTS) IN WHICH THE FIRST D.A.T. WAS POSITIVE

Age at Onset (decade)		0-9	10-19	20-49	50+
Percentage Change in Functional Status	Improved	100	90	16·6	36·8
	Unchanged	0	0	16·6	21·1
	Worse	0	10	50	12·2
	Total	3	10	12	19
Mean Functional Status	When First Seen	1	2·8	3·8	3·9
	At Fourth Follow-up	4·3	4·7	4·1	4·0

TABLE IV

CHANGE IN FUNCTIONAL STATUS AT FOLLOW-UP IN EARLY CASES (CHILDREN AND ADULTS) IN WHICH THE FIRST D.A.T. WAS NEGATIVE

Age at Onset (decade)		0-9	10-19	20-49	50+
Percentage Change in Functional Status	Improved	86	81·5	56	77
	Unchanged	5·5	18·5	38	0
	Worse	8·5	0	6	23
	Total	36	27	16	13
Mean Functional Status	When First Seen	2·0	3·1	4·2	3·6
	At Fourth Follow-up	4·4	4·7	4·7	4·2

There is little difference in prognosis between the "positive" and "negative" groups.

Fig. 5 (opposite) illustrates the reason for the apparently greater improvement of the juvenile group. When first seen, those in the younger decades had a low functional status and improved a great deal during the 4 years. Those in the older decades started with a higher functional level and achieved almost the same functional state at the fourth year.

The reason for the marked difference in functional status when first seen between juveniles and adults may be due to the fact that most adults have responsibilities, either in employment or in looking after a home and family, and therefore keep active longer; children, on the other hand, are nearly

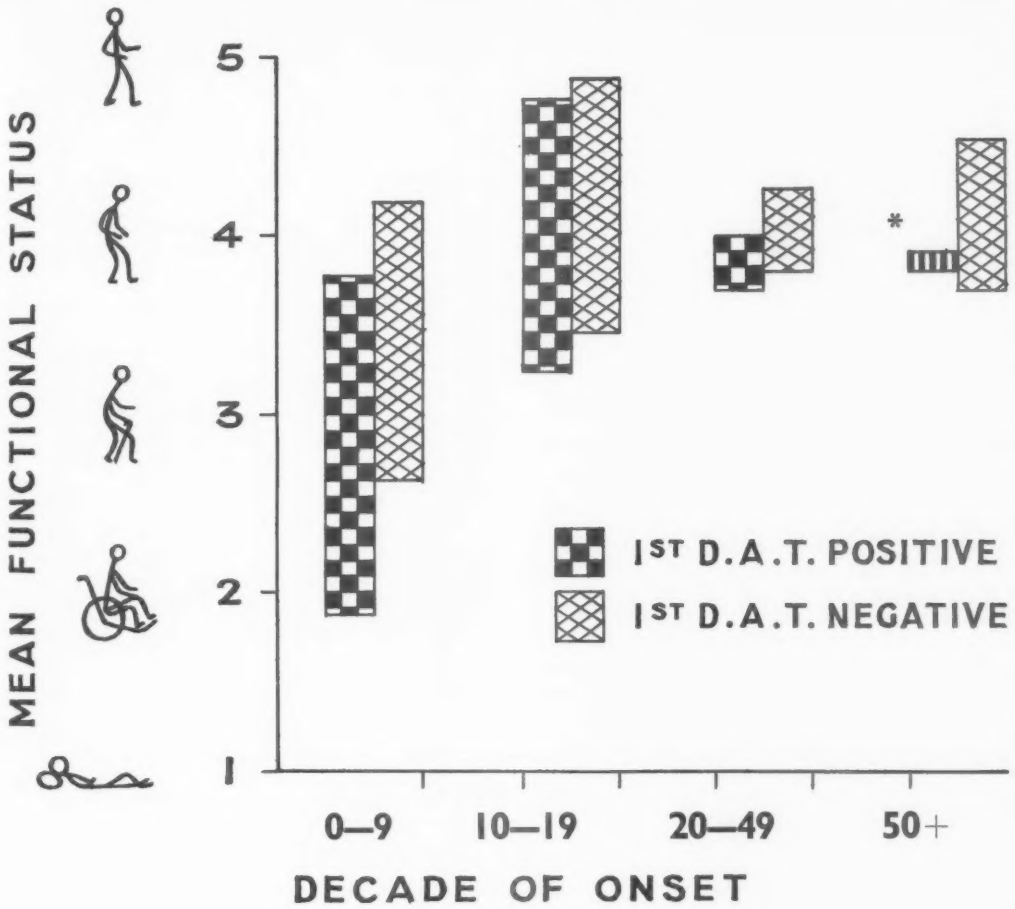

Fig. 5.—Improvement or deterioration* of mean functional status over a 4-year period, according to decade of onset and D.A.T. in a series of 282 cases.

always put to bed when the early signs of illness appear. Our experience in this Unit has been that prolonged rest and immobilization, particularly in children, reduces them to a condition of stiffness and eventual ankylosis, with a consequent low functional state.

Summary

140 adult patients with rheumatoid arthritis were compared with the 142 juvenile patients used for the study described in the previous paper (Bywaters, Carter, and Scott, 1959). Both groups were comparable as regards criteria and duration of follow-up, but fewer D.A.T.s were done in the adult group; therefore only the first D.A.T. was used for comparison between the two groups of patients. A partially different group of adults (71) was used in compiling Figs 1 and 2, which show that the D.A.T. becomes progressively positive with greater age at onset, and that there is a progressive increase in the frequency of high titres with age. A marked difference is seen in the D.A.T. response of the adult and juvenile group, 50 per cent. of adults being sero-positive on first testing compared with 13·4 per cent. of juveniles. A progressive change with age in D.A.T. response and incidence of rash and nodules is also seen.

Improvement is more marked in the young, because children tend to start at a lower functional grade than adults. There is no significant difference in prognosis between the sero-positive and sero-negative groups in either children or adults.

Since there is progressive change with age in the clinical features here investigated, we conclude that there is not yet sufficient evidence to justify the view that rheumatoid arthritis and Still's disease are

separate diseases. It is suggested that the differences are due to age alone.

We are most grateful to Dr. E. Lewis-Faning for his detailed criticisms and suggestions in regard to the presentation of these results.

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Comparaison des titres d'agglutination différentielle (D.A.T.) dans l'arthrite rhumatismale juvénile et adulte

RÉSUMÉ

On compara 140 cas d'arthrite rhumatismale adulte à 142 cas juvéniles, ayant déjà fait l'objet d'un travail antérieur (Bywaters, Carter, et Scott, 1959). Les deux groupes sont comparables en ce qui concerne les critères diagnostiques et la durée d'observation, mais le D.A.T. fut déterminé moins souvent chez les adultes; pour cette raison on ne s'est servi que de la première détermination pour comparer les deux groupes. On prit un groupe partiellement différent d'adultes (71) pour compiler les fig. 1 et 2, montrant que la positivité du D.A.T. augmente en fréquence avec l'âge de début et le titre tend à monter avec l'âge du malade. On nota une différence marquée dans le D.A.T. entre les deux groupes, 50% des adultes ayant été séro-positifs à la première détermination. comparé à 13,4% des jeunes. On observa aussi des altérations progressives, selon l'âge, du D.A.T. et de la fréquence de l'exanthème et des nodules.

Les améliorations furent plus marquées chez les jeunes, parce que les enfants tendent à commencer à un grade fonctionnel plus bas que les adultes. Il n'y eut pas de différence pronostique significative entre les groupes séro-positifs et séro-négatifs, jeunes ou adultes.

En raison des altérations progressives des traits cliniques selon l'âge, observées dans ce travail, on conclut qu'il n'y a pas de preuves suffisantes pour justifier le point de vue que l'arthrite rhumatismale et la maladie de Still soient des maladies séparées. On suggère que les différences notées ne seraient dues qu'à l'âge.

Comparación de cifras de aglutinación diferencial (D.A.T.) en la artritis reumatoide juvenil y adulta

SUMARIO

Se compararon 140 casos de artritis reumatoide adulta con 142 casos juveniles, objetos de un trabajo anterior (Bywaters, Carter y Scott, 1959). Ambos grupos se parecen respecto a los criterios diagnósticos y al período de observación, pero el D.A.T. fué determinado con menos frecuencia en los adultos; por esta razón, para comparar los grupos entre si, se tomó sólo la primera determinación. Se escogió un grupo parcialmente diferente de adultos (71) par componer las Figs. 1 y 2. revelando que la positividad de D.A.T. aumenta en frecuencia con la edad de comienzo de la enfermedad y que sus cifras tienden a subir con la edad del enfermo. Se notó una diferencia marcada en la D.A.T. entre los dos grupos, un 50% de los adultos y sólo un 13,4% de los jovenes siendo sero-positivos a la primera determinación. Se observaron también alteraciones progresivas, según la edad, de la D.A.T. y de la frecuencia de exantemas y de nódulos.

Mejorías fueron más acentuadas en los jóvenes, ya que niños tienden a empezar con un grado funcional más bajo que los adultos. No hubo diferencia pronóstica significativa entre los grupos sero-positivos y los sero-negativos tanto jóvenes como adultos.

En vista de las alteraciones progresivas de los rasgos clínicos con la edad, observadas en este trabajo, se concluye que no hay datos suficientes para justificar la hipótesis, que la artritis reumatoide y la enfermedad de Still sean enfermedades separadas. Se sugiere que las diferencias notadas se deberían sólo a la edad.

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URINARY EXCRETION OF ACID POLYSACCHARIDE IN RHEUMATOID ARTHRITIS AND OTHER DISEASES

BY

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The excretion of acid mucopolysaccharide in the urine was described by Kerby (1954), using a method devised by Astrup (1947) for the estimation of heparin. Scott (1955) introduced the precipitation of acid mucopolysaccharides by quaternary ammonium salts; this method was adapted to urine by Di Ferrante and Rich (1956a, b). Di Ferrante (1957) found that patients with rheumatoid arthritis showed increased excretion of acid mucopolysaccharide when compared with normal controls. Di Ferrante, Robbins, and Rich (1957) described similar excess excretion in cases of disseminated lupus erythematosus. It was concluded (Rich, Di Ferrante, and Archibald, 1957) that "the urinary excretion of acid polysaccharide is elevated in several diseases associated with abnormal metabolism of mucopolysaccharide-rich connective tissues". It was therefore decided to compare the excretion of acid mucopolysaccharide in patients with rheumatoid arthritis with that in patients suffering from various other maladies, and to define, by isolation of the material, the type of acid polysaccharide in each particular specimen of urine, in order to explore possible differences and to give some idea of the origin of the material. Pooled samples were collected for more extensive analysis.

Materials and Methods

24-hour samples of urine were collected from patients in hospital. Most of the patients with rheumatoid arthritis had clinically active disease and a raised erythrocyte sedimentation rate, and the majority of the adult patients had a positive Rose-Waaler test. The urines were kept, without preservative, at 4° C. 500 ml. urine was used for each estimation.

The method used for the isolation of acid mucopolysaccharide was similar to the modification by Meyer, Grumbach, Linker, and Hoffman (1958) of the method of Di Ferrante and Rich (1956b). Samples with a specific gravity of 1,020 or more were diluted with an equal volume of water. The urine was filtered and acidified to pH 6·0 and a warm aqueous 5 per cent. solution of cetyl trimethylammonium bromide was added (1·7 ml./100 ml. urine). After standing overnight at 4° C., the solution was centrifuged in the cold. The precipitate was washed three times in a large volume of ethanol. The material insoluble in ethanol was dissolved, with agitation and warming to 37° C., in a small volume of 10 per cent. aqueous sodium acetate, and the pH was adjusted to 9·0. Insoluble material was centrifuged down and re-extracted with water. The combined supernatant was acidified to pH 5·0. The crude acid polysaccharide was then precipitated with 1·5 volumes of ethanol and left at 4° C. overnight. This was centrifuged and the precipitate washed with 80 per cent. ethanol. It was extracted with a small volume of water and centrifuged at high speed. To the clear solution, calcium acetate and acetic acid were added to final concentrations of 5 per cent. and 0·5 N, respectively. The solution was fractionally precipitated with alcohol, according to the method of Meyer, Davidson, Linker, and Hoffman (1956). Resulting fractions were washed in increasing concentrations of alcohol and dried in ether, and this was followed by desiccation over phosphorus pentoxide. Each sample was weighed and analysed for uronic acid both by the orcinol method and by Dische's carbazole method. All methods of analysis were as used by Loewi and Meyer (1958), and described by Meyer and others (1956) and Rapport, Meyer, and Linker (1951).

To obtain purified material for analysis, urine pools of about 10 l. were collected. After isolation by the above procedures, the material was dissolved in water and digested with pepsin for 24 hrs, followed by trypsin for a similar period. The material was reprecipitated and subjected to the procedure of Sevag (1934). After another precipitation, treatment with kaolin and Lloyd's reagent was carried out, and finally Dowex 50 (H^+) was used. The method is essentially that used by Meyer and others (1956).

Results

Table I shows the results of estimations of acid mucopolysaccharide in the urines of 73 individuals. Since the carbazole values differed somewhat from sample to sample, the amounts of polysaccharide found were adjusted by calculation to a carbazole value of 20 per cent. in each case, so that comparison could be made. The actual readings were nearly all close to this figure. In all cases, rheumatoid and others, acid polysaccharide was precipitated at between 40 and 50 per cent. ethanol concentration, and gave a ratio of carbazole to orcinol close to 1·0, indicating chondroitin sulphate A or C. Though some adult cases of rheumatoid arthritis showed high excretion values, others showed values similar to those found in other diseases and in normal controls. The difference between female rheumatoid arthritics and normal controls approached significance ($P = <0{\cdot}10, >0{\cdot}05$). Eight cases showed a daily excretion of more than 19 mg. acid mucopolysaccharide. These included four cases of rheumatoid arthritis, one of which was complicated by pyelo-nephritis, three cases of epilepsy, and one of pneumonia. Excretion of less than 1 mg./24 hrs was seen in two cases of rheumatoid arthritis complicated by amyloidosis. In the children studied, excretion of acid polysaccharide in rheumatoid arthritis was similar to that occurring in other diseases, but significantly lower than that found in normal controls ($P = 0{\cdot}01$). The figure taken for any particular patient was the first one obtained after admission, though, in most cases, several estimations were made subsequently. In two patients, in each of whom daily estimations were done on six consecutive days, the day-to-day variations were found to be relatively small (3·1 mg. with a standard deviation of ±0·65 in one case and 12·4 mg. with S.D. ±2·38 in the other). The majority of the figures were lower than those obtained by Di Ferrante (1957); the reason for this may be sought in differences in the techniques used, since, in the present investigation, it was decided to sacrifice completeness of recovery to removal, as far as possible, of non-acid mucopolysaccharide material. Using the almost identical method, Meyer and others (1958) obtained figures for normal controls which are similar to those reported here.

Table II shows figures for acid mucopolysaccharide excretion in four patients before and during salicylate administration. In two cases a fall was recorded, while in one (Case 4) a rise in excretion

TABLE II

EFFECT OF ADMINISTRATION OF SALICYLATES ON EXCRETION OF ACID MUCOPOLYSACCHARIDE (APS) IN FOUR CASES OF RHEUMATOID ARTHRITIS

Case No.	APS (mg./24 hrs)		Change while taking Salicylates
	Control Period	Salicylate (4–5 g./day)	
1	8·7; 9·0	3·5; 3·8; 2·6; 2·2; 3·1; 3·0	Fall followed by Rise
2	25·4; 21·3	12·3; 9·4	Fall
3	9·3; 10·2	14·2; 2·0	Fall
4	5·6; 6·3	12·0; 17·9	Rise

TABLE I

MEAN URINARY EXCRETION OF ACID MUCOPOLYSACCHARIDE (APS) IN CHILDREN AND ADULTS WITH VARIOUS DISORDERS (mg./24 hrs, 20 per cent. Carbazole)

Series			Age (yrs)	Condition					
				Rheumatoid Arthritis	Other Diseases*	Connective Tissue Disorders other than Rheumatoid Arthritis	Epilepsy	Normal	Rheumatoid Arthritis with Amyloidosis
Children		No. of Cases ..		10	10	5	2	8	0
		Mean	9	5·81±2·66	6·82±13·92	2·96±2·84	26·9 and 31·6	13·55±7	—
		Range	3 to 15	3 to 10·3	0·9 to 36·8	0·9 to 6·5	—	6·1 to 24	—
Adults	Females	No. of Cases ..		12	4	0	1	9	1
		Mean	34·3	16·14±17·12	5·55±6·45	—	19·15	6·57±2·9	<1·0
		Range	16 to 63	3·1 to 59	1·9 to 15·1	—	—	2·5 to 12·9	—
	Males	No. of Cases ..		4	2	1	1	8	1
		Mean	29	8·75±1·73	8·6 and 1·0	1·0	14·2	6·88±5·1	<1·0
		Range	17 to 50	6·2 to 10	—	—	—	2·7 to 17·2	—

* Tuberculosis, nephritis, pneumonia, appendicitis.

occurred, although this patient's temperature became normal and the erythrocyte sedimentation rate was falling during the administration of salicylate. Case 3 showed an initial rise, followed by a fall in acid polysaccharide excretion.

The purified acid polysaccharide obtained from large volumes of normal and rheumatoid urine was analysed (Table III). Precipitation by ethanol began at 40 per cent., and was complete at 50 per cent. In the two purified samples cited in Table III, the only amino-sugar found chromatographically was galactosamine, suggesting a chondroitin sulphate. When, however, less highly purified material was subjected to this procedure, a weak glucosamine spot was also obtained. This suggests a relatively small amount of hyaluronic acid or of keratosulphate, but the presence of some glucosamine-containing protein cannot be excluded. The high Dische (carbazole) to orcinol ratio is indicative of chondroitin sulphate A or C; rotational values are suggestive of chondroitin sulphate C and digestion by testicular hyaluronidase (reductimetric method, 24-hr incubation) also suggests chondroitin sulphate A or C rather than B, since the latter is not hydrolysed by this enzyme. That the substance is not chondroitin sulphate B is further shown by the relatively high ethanol solubility, the high ratio of Dische to orcinol value (chondroitin sulphate B gives a ratio of around 0·5) and the low rotation. Precipitation at 40-50 per cent. ethanol and the rotation figures are suggestive of chondroitin sulphate C rather than A. In the absence, however, of an infra-red pattern and of material sufficiently pure for this investigation to be carried out, such differentiation between chondroitin sulphate A and C cannot be made with any degree of assurance.

Discussion

This investigation was undertaken first to determine the exact nature of the acid polysaccharide excreted in rheumatoid arthritis and other diseases, and, secondly, to discover whether the increased excretion, as reported by Di Ferrante (1957), was peculiar to rheumatoid arthritis or was also encountered in unrelated diseases.

The same type of chondroitin sulphate was discovered in all specimens of urine examined in this investigation and the full analysis of pooled material reported in Table III confirmed this. Di Ferrante and Rich (1956a) showed that normal urine contained chondroitin sulphate A or C, and Di Ferrante (1957) indicated that the material obtained from pooled rheumatoid urine was similar, and could be depolymerized by hyaluronidase. Di Ferrante (1957) also reported the presence of some hyaluronic acid in the urinary acid polysaccharide. I have found no evidence of this in the purified material. A trace of glucosamine was found, however, when less highly purified material was examined. Urine from a case of Marfan's syndrome (personal observation) showed no abnormal constituents qualitatively or quantitatively. Material isolated in the present investigation from patients with epilepsy who were taking hydantoin proved to be, as in the rheumatoid and normal cases, chondroitin sulphate A or C.

With regard to the origin of this urinary constituent, Kerby (1954) showed that acid mucopolysaccharide was present in urine in the renal pelvis and that the urinary content was not raised by prostatic massage. Badin, Schubert, and Vouras (1955) obtained evidence of the presence in increased amount of a similar substance in plasma from cases of rheumatoid arthritis. One may assume, therefore, that urinary chondroitin sulphate is derived from plasma by renal excretion. Meyer (1957), discussing the distribution of acid mucopolysaccharides in various tissues, lists chondroitin sulphate A and/or C as occurring in cartilage and bone. These two tissues must, therefore, be considered as possible sites of origin of the urinary acid mucopolysaccharide, and both cartilage destruction and osteoporosis are indeed found in rheumatoid arthritis. It was noticed, however, that

TABLE III

ANALYTICAL DATA FOR URINARY ACID MUCOPOLYSACCHARIDE

Urine		N	Hexosamine		Uronic Acid (per cent.)		$[\alpha]^D$	Digestion with Testicular Hyaluronidase
Source	Amount (mg.)	(per cent.)	Per cent.	Type	Orcinol	Dische		
Rheumatoid Arthritis	28·0 (50 per cent. Ethanol)*	3·5	20·8	Galactosamine	18·6	28·6	−5°	+
Normal	16·5 (50 per cent. Ethanol)*	−†	21·0	Galactosamine	18·0	29·1	−17°	+

* Percentage at which precipitate obtained.
† Inadequate material for estimation

cases of rheumatoid arthritis with extensive osteoporosis and a case of Cushing's disease did not have an unduly great excretion. Similarly, activity of the disease did not correlate with the amount of acid mucopolysaccharide excreted. It is also not possible to account on such a basis for the relatively high levels of excretion shown by some epileptics.

When the quantitative excretion figures were examined, much overlap was found between rheumatoid arthritics, patients with other diseases, and normal controls. Owing to the very wide ranges of readings in each of these categories, no statistically significant differences were found. The reason for these wide variations is apparently not to be sought in the techniques employed, since repeated readings on single patients did not show such variations. Several of the adult patients with rheumatoid arthritis excreted abnormally large amounts of acid polysaccharide, while others excreted only small amounts. The distribution showed no constant relationship to activity of the disease, as assessed by the erythrocyte sedimentation rate. Many of the patients were receiving salicylates and other forms of treatment, which may have caused a decrease in the amount excreted; Di Ferrante (1957) observed such an effect, and a fall occurred in three out of four patients on salicylates, as recorded in Table II. There were, however, some patients who showed a low excretion in the absence of drug therapy. The low level of excretion of acid polysaccharide in children with rheumatoid arthritis may be the result of interference with skeletal growth. Such an explanation is also suggested by the significantly greater excretion in normal children when compared with normal adults ($P = <0{\cdot}02$, $>0{\cdot}01$). This latter finding was also noted by Rich and others (1957). Relatively high excretion was found in cases of epilepsy receiving hydantoin and in a case of pneumonia (normal controls of comparable age showed much lower excretion). In two cases of rheumatoid arthritis complicated by extensive amyloidosis involving the kidneys, excretion of acid polysaccharide was particularly low. Craddock and Kerby (1955) found decreased excretion in cases of diabetes with renal complications. Patients with other disorders involving connective tissue, such as rheumatic fever and dermatomyositis, did not show high urinary acid polysaccharide excretion. Di Ferrante and others (1957) reported a raised level of excretion in disseminated lupus erythematosus. The failure to demonstrate a high level of acid polysaccharide excretion in many cases of rheumatoid arthritis, although the disease was active, and failure to demonstrate raised levels in some other connective tissue disorders, suggest that the statement by Rich and others (1957) that "the urinary excretion of acid polysaccharide is elevated in several diseases associated with abnormal metabolism of mucopolysaccharide-rich connective tissues" needs qualification. The results of the present investigation do not suggest that urinary acid polysaccharide excretion constantly mirrors any such abnormality in the tissues, such as might occur in the rheumatic diseases. To date, evidence for such a disorder has only been found in gargoylism, which shows high urinary acid polysaccharide excretion (Meyer and others, 1958).

Summary

Acid mucopolysaccharide has been estimated in the urine of patients with rheumatoid arthritis and with other diseases, and in normal controls. A raised level of excretion was found in some adult patients with rheumatoid arthritis, while others showed normal or low levels. No rise was found in patients with rheumatic fever and dermatomyositis, but a few patients with other diseases showed raised levels of excretion. In children, the excretion was less in rheumatoid arthritics than in normal controls. The acid mucopolysaccharide in all cases was found to be chondroitin sulphate A or C.

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Excrétion urinaire de polysaccharide acide dans l'arthrite rhumatismale et dans d'autres maladies

RÉSUMÉ

On détermina le mucopolysaccharide acide chez des malades atteints d'arthrite rhumatismale et d'autres affections, ainsi que chez des témoins. On en trouva un taux élevé chez quelques adultes atteints d'arthrite rhumatismale, mais chez d'autres ce taux fut normal ou bas. On ne trouva pas de taux augmentés chez des malades atteints de rhumatisme articulaire aigu ou de dermatomyosite, mais on les observa chez quelques autres malades. Chez des enfants rhumatisants arthritiques il y eut une diminution du taux, absente chez des enfants normaux. Dans tous les cas on identifia

le mucopolysaccharide acide comme sulfate de chondroïtine A ou C.

Excreción urinaria de polisacarido ácido en la artritis reumatoide y otras enfermedades

SUMARIO

Se determinó el mucopolisacarido ácido en la orina de enfermos con artritis reumatoide, con otras enfermedades y en la de testigos. Se halló una tasa elevada en algunos adultos con atritis reumatoide, pero en otros ésta fué normal o baja. No hubo aumento en enfermos con reumatismo poliarticular agudo o con dermatomiositis, pero se observó una tasa aumentada en algunos otros enfermos. En niños reumatoideo-artriticos la excreción fué disminuida en comparación con la de niños normales. En todos los casos se identificó el mucopolisacarido ácido como sulfato de condroitina A o C.

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CONTROLLED TRIAL OF G27 202 (p-HYDROXYPHENYLBUTAZONE) IN RHEUMATOID ARTHRITIS

BY

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Two metabolites were isolated from the urine of patients taking phenylbutazone by Burns, Rose, Goodwin, Reichenthal, Horning, and Brodie (1955); these metabolites were found to be identical with two pyrazole compounds synthesized in Switzerland by Pfister and Häfliger (1957) and Denss, Häfliger, and Goodwin (1957), which were called respectively G27 202 (p-hydroxyphenylbutazone) and G28 315, the latter being a potent uricosuric agent. Experiment had shown that G27 was an anti-inflammatory agent equal in potency to phenylbutazone but producing few of the side-effects commonly associated with this drug. When G27 became available for clinical trial, it was decided to test its effect in rheumatoid arthritis. Hart and Burnley (1959) have reported its effects in a number of conditions, Vaughn, Howell and Kiem (1959) have reported the results of a trial in which it was compared with steroids, aspirin, and phenylbutazone in patients with rheumatoid arthritis.

The present investigation has been conducted as a double-blind trial, using G27 and a bland tablet; in this way it was hoped to show whether G27 possessed anti-rheumatic as well as anti-inflammatory properties or whether it was merely another comparatively non-toxic analgesic.

Method

Thirty patients were taken, all suffering from rheumatoid arthritis, as defined by the American Rheumatism Association (Steinbrocker, Traeger, and Batterman, 1949) of varying severity and duration.

Fifteen received tablets of G27 (200 mg. twice daily with or after food), and the other fifteen received bland tablets identical in size, shape, and colour, and supplied in identical bottles. The allocation and distribution of the tablets was completely randomized, and this, together with the dispensing of the tablets, was carried out by colleagues in no way associated with the trial. The code was held by another doctor in the clinic, so that in the event of an emergency (as for example, the suspicion of agranulocytosis), advice with regard to treatment was available without upsetting the trial as a whole. In fact, no such emergency arose during the trial. The patients were asked if they would co-operate in the trial of a new drug which might or might not help them and which might produce side-effects; they were not told that two different sets of identical tablets were being used, nor were they told that at the end of the trial period of 6 weeks those taking the control tablets would be automatically switched to G27. In this way, it was hoped to eliminate any possible bias in the patient towards a new drug.

No patients who were being given steroids or gold injections were included in the trial. The patients were asked during the 6-week trial not to take any other tablets whatsoever unless they felt that their condition was deteriorating, in which case they were asked to take aspirin, and to note the amount taken each day. As far as possible they were seen for clinical assessment and blood test each week. For the assessment of disease activity, etc., the three worst joints, as indicated by the patient, were taken as representative of the whole, and tenderness, pain, and swelling, were estimated on these joints alone throughout the trial.

Results

The trial was kept up until every patient had completed 6 weeks' treatment and all the blood tests and blood level estimations were available. Five patients in all failed to complete the trial. One in the G27 group developed pneumonia after 2 weeks, up to which time he had reported good progress, and four in the control group, all of whom tolerated the tablets for 3 or 4 weeks, asked to be allowed to go back to the previous treatment because they felt their condition to be deteriorating. Three of these four patients were, in fact, persuaded to continue for a further week, and during that week they were changed to G27 from the control tablets without their knowledge; two reported great improvement during that week and have since continued with G27 with benefit.

Routine weekly testing of the urine for sugar and albumin showed five cases of transient albuminuria in the G27 group and three in the control group; this may have been due to the sensitive method of testing used and, as in no case was it persistent, a full renal investigation was not carried out. No change in blood pressure was recorded in either group.

The chief results are shown in Table I:

Body Weight.—The slight increase in weight of the patients on G27 suggests some fluid retention, and this confirms the findings of Vaughn and others (1959), but when it is remembered that swelling of the feet was not recorded in any patient on G27 the gain in weight should not be regarded as a serious complication.

Morning Stiffness.—One of the interesting features of this trial was that the patients on G27 experienced a considerable reduction in the degree of morning stiffness; this symptom is notoriously difficult to eradicate and subsequent experience with the drug has confirmed that patients frequently report loss of, or considerable reduction in, the degree of morning stiffness. Table I shows that almost 50 per cent. of the patients on G27 lost their stiffness, compared with only one in the control group. The Table also records the number of patients who found it necessary to take aspirin, and it can be seen that the reduction in stiffness cannot be accredited to the aspirins taken.

Strength of Grip.—This was measured in the customary way by recording the highest reading when a sphygmomanometer cuff was blown up to a pressure of 30 mm. Hg and squeezed as hard as possible. The G27 group showed a considerable improvement over the controls. A crude estimate of the degree of fist closure was made in all cases, and in spite of the crudity of this test, seven cases in the G27 group showed an increase compared with only two in the controls, the remainder being the same or worse.

Pain.—This was estimated in degrees from one to three, by registering the patient's impression and by checking the number of aspirin the patient found it necessary to take. When measured in degrees, the total score of each group at the start of the trial was at the maximum of 45, the G27 group fell to 21, and the controls to 41. The Table shows the individual response and the number

TABLE I

SUMMARY OF CLINICAL RESULTS

Clinical Findings		Series	
		G27 202	Control
Body Weight (lb.)	Increase	8 (mean 1·6)	2 (mean 0·4)
	Decrease	5 (mean 1·8)	9 (mean 2·0)
	No change	1 —	0 —
	Patient withdrew	1 —	4 —
Morning Stiffness	Lost	7 (1)*	1 (1)*
	Much less	5 (1)*	0 —
	No change	2 (2)*	14 (13)*
	Patient withdrew	1 —	0 —
Strength of Grip (mm. Hg) in Each Hand	Increase	21 (mean 36)	6 (mean 15)
	Decrease	7 (mean 13)	15 (mean 20)
	No change	2 —	9 —
Pain	Lost	6	0
	Much less	4 (1)*	3 (3)*
	No change	5 (3)*	12 (11)*
Tenderness	Lost	6	1 (1)*
	Better 50 per cent.	4 (2)*	3 (2)*
	Better 25 per cent.	4 (2)*	2 (2)*
	No Change or Worse	1	8 (8)*
	Patient Withdrew	0	1
Swelling	Lost	4	1
	Better 50 per cent.	8	2
	Better 25 per cent.	1	2
	No change or Worse	2	10
Subjective Assessment	Better	12 (1)*	3 (2)*
	No change or Worse	3 (3)*	12 (12)*
Resort to Aspirin	None	11	1
	Half Dose	3	4
	No Change or More	1	10

* Number of patients who resorted to aspirin.

of aspirin taken by each group, and these results suggest that G27 must have considerable analgesic properties.

Tenderness.—This was gauged by recording the patients' reaction to finger pressure and the total scores were, in the G27 group, 102 at the start and 33 after 6 weeks, and in the control group, 99 at the start and 79 after 6 weeks.

Swelling.—When the foregoing result is taken together with the total scores resulting from the estimates of swelling, which were 78 to 31 in the G27 group and 78 to 69 in the controls, there is some evidence to suggest clinically that G27 has some anti-inflammatory properties.

Subjective Assessment.—At each visit the patients were questioned as to their ability to walk, to dress themselves, to do housework, to shop for themselves, to bath, and to go upstairs, and at the end of the trial a greater number of the G27 group were able to do more things than of the control group, who, if anything, had tended to get worse.

A factor seldom regarded as statistically significant but one which is clinically interesting, is the patient's opinion of the treatment. When it is borne in mind that none of these patients knew that control tablets were included in the trial, it is interesting to find that twelve of the fifteen on G27 said they felt better at the end of the trial, and that twelve of the fifteen controls said that they felt the same or worse.

Complications.—In view of the multiplicity of complications recorded when phenylbutazone is used, even the slightest unusual feature noted by the patients was recorded, and they were directly questioned about the side-effects usually said to be associated with phenylbutazone. None of the side-effects noted were persistent, and the majority cleared by the time the patient attended in the following week. At no time was it necessary to consider stopping the drug because of side-effects. Diarrhoea and loose motions and occasional transient pruritus seemed to be the side-effects most commonly complained of, but they all cleared rapidly in spite of continued treatment at the same dosage. A greater variety of side-effects was found amongst the control group (Table II). 6 weeks is far too short a period in which to decide whether side-effects result from the use of a new drug, but subsequent experience confirms the impressions already reported by Hart and Burnley (1959) and Vaughan and others (1959) that G27 appears to be free from serious side-effects.

TABLE II
SUMMARY OF TRANSIENT COMPLICATIONS

Side-Effects	Series	
	G27 202	Controls
Indigestion or Heartburn ..	4	4
Diarrhoea and Loose Motions ..	5	2
Ulcers of Mouth	3	2
Pruritus or Urticaria	6	3
Swelling of Feet	0	2
Giddiness	1	1
Epistaxis	0	1
Depression	1	0
Poor Appetite	0	2
Headache	1	1
Total Complications ..	21	18

Blood Investigations.—At each weekly visit the haemoglobin, the total and differential white cell counts, and the erythrocyte sedimentation rate were estimated. A comparison between the levels seen at the start and the end of the trial is shown in Table III.

Liver function tests were carried out at the start and at the end of the trial in over half of the cases, and G27 blood level estimations were made at least once in each patient during the trial. This last investigation was carried out on both controls and

TABLE III
SUMMARY OF LABORATORY FINDINGS

Result			Increase		Decrease		No Change		Not Tested	
Series			G27	Control	G27	Control	G27	Control	G27	Control
Laboratory Test	Haemoglobin	No. of Cases	4	4	9	6	1	1	1	4
		Mean Change (per cent.) ..	3	6	6	9	—	—	—	—
	Erythrocyte Sedimentation Rate	No. of Cases	10	5	3	5	1	1	0	4
		Mean Change (mm./hr) ..	7	8	4	11	—	—	—	—
	White Cell Count	No. of Cases	9	3	3	8	2	0	0	4
		Mean Change	900	1,000	500	900	—	—	—	—

G27 patients, and in this way a check was available to show whether any patient had been given the wrong tablets. In fact, no G27 was found in the blood of the controls. The blood picture showed little difference between the two groups, and there was little variation from week to week; at no stage did a fall occur in the circulating polymorphonuclear leucocytes. Liver function tests, although by no means normal in themselves, especially with regard to thymol turbidity and zinc sulphate levels at the start of the trial, showed no difference between the groups after 6 weeks.

With regard to the blood levels of G27, the average level when 400 mg. daily was taken was 11·2 mg. per cent. (range 6 to 17 mg. per cent.). This is high when compared with blood Butazolidin levels and suggests a good rate of absorption from the gut. From results obtained since the conclusion of the trial, it appears that G27 is rapidly both absorbed and excreted; a level as high as 18 mg. per cent. was registered 48 hrs after starting the drug, and on another occasion the level had dropped to 2 mg. per cent. within 48 hrs of stopping it. One of the difficulties encountered in estimating G27 levels is that there is very little difference between the wave bands of G27 and Butazolidin, but as it is unlikely that both drugs will be administered at the same time, and provided 2 to 3 weeks is allowed for any Butazolidin to clear from the blood stream before the G27 levels are estimated, there is little likelihood of confusion. Codeine and salicylates when given in a a large enough dosage may also lead to confusion, but the wave bands of all these drugs are quite distinct.

Correlating the height of the blood level and the incidence of side-effects showed no obvious trend towards the assumption that the higher the level, the more frequent the complications, but a much greater series and much higher levels must be obtained before this can be proven. However, in the three cases that showed levels of above 15 mg. per cent. no side-effects were reported at all.

Summary

The results are reported of a blind trial of G27 202. Half of thirty patients suffering from rheumatoid arthritis were given 400 mg. G27 202 daily, and half were given placebo tablets for a period of 6 weeks. There was definite improvement in strength of grip, morning stiffness, pain, tenderness, and swelling in those taking G27 202 in comparison with those taking the control tablets. It is suggested, in view of these findings, that G27 202 has analgesic and anti-inflammatory properties equal to those of phenylbutazone but not associated with any of the side-effects seen with the latter drug. The fact that the erythrocyte sedimentation rate showed no alteration suggests that G27 202 has little if any anti-rheumatic potency, but it is felt that this drug should be seriously considered as an alternative therapeutic agent in the treatment of rheumatoid arthritis.

I should like to express my thanks to Dr. W. Stoddart for his help and encouragement, to Dr. A. L. Miller and his Staff both at the Middlesex Hospital and the Arthur Stanley Institute for their help and co-operation with blood investigations and levels, and to Messrs. Geigy Ltd. for the generous supplies of G27 202 used throughout the trial.

DISCUSSION

DR. O. SAVAGE (*London*) congratulated Dr. Cardoe on his report. The fact that this was a carefully planned trial with double blind control emphasized how few objective measurements we had in rheumatoid arthritis. Morning stiffness, pain, and tenderness were subjective, and even the grip test was not entirely objective. He felt that, with an increasing number of drugs available for the treatment of rheumatoid arthritis, the question which was the best would remain uncertain until the objective methods of assessing the disease were improved.

DR. J. J. R. DUTHIE (*Edinburgh*) asked whether G27 202 was a better analgesic than aspirin.

Another speaker asked if temperatures were taken.

PROF. S. J. HARTFALL (*Leeds*) asked if there were more toxic reactions amongst treated than amongst control cases, and whether the number of placebo reactors had been determined.

DR. CARDOE replied that G27 202 was about as good an analgesic as aspirin or phenylbutazone, but not so efficient as aspirin as an anti-rheumatic agent. Temperatures had not been taken. Erythrocyte sedimentation rates remained abnormal in both the treated and the control groups.

Placebo reactors had not been especially looked for, but he had noted that oral ulcers, usually considered to be a toxic effect of phenylbutazone, had been equally frequent in each group.

DR. M. F. MCMAHON (*Cork*) said that he had conducted a controlled trial of G27 202 in 120 patients and had noted that mouth ulcers and pruritus were more common amongst the controls. In his series, two out of forty, who had both drugs, asked to stop G27 202 and to take phenylbutazone instead, because they considered it more effective.

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Essai contrôlé de G27 202 (p-hydroxyphénylbutazone) dans l'arthrite rhumatismale

RÉSUMÉ

On relate les résultats d'une étude comparée de G27 202. Pendant six semaines on traitait trente malades atteints d'arthrite rhumatismale; à quinze d'entre eux on administrait 400 mg. de G27 202 par jour et aux autres quinze on donnait des comprimés inertes. On a constaté une amélioration définie dans la force de la poigne, enraidissement matinal, douleur, sensibilité et gonflement chez les malades traités par G27 202, contrastant avec la condition de ceux recevant la médication-témoin. On suggère, par conséquent, que le G27 202 a des propriétés analgésiques et anti-inflammatoires égales à celles de la phénylbutazone, sans exercer les effets secondaires de celle-ci. Le fait que la vitesse de sédimentation érythrocytaire demeurait la même, suggère que le G27 202 a un pouvoir antirhumatismal faible ou nul; on pense, toutefois, que ce médicament mérite une considération sérieuse comme agent thérapeutique alternatif dans l'arthrite rhumatismale.

Ensayo controlado de G27 202 (p-hidroxifenilbutazona) en la artritis reumatoide

SUMARIO

Se relatan los resultados de un ensayo controlado de G27 202. Se trataron treinta enfermos con artritis reumatoide durante 6 semanas; a una mitad de ellos se administraron 400 mg. de G27 202 diarios, mientras que la otra mitad recibió comprimidos de control. Una mejoría definida en la fuerza del apuñamiento, rigidez matinal, dolor, sensibilidad e hinchazón fué observada en los enfermos tratados con G27 202, contrastando con la condición de los tratados con los comprimidos de control. Se sugiere, en vista de estos resultados, que G27 202 posee propiedades analgésicas y anti-inflamatorias iguales a las de la fenilbutazona, sin ejercer los efectos secundarios de ésta. El hecho de que la velocidad de sedimentación eritrocitaria quedó sin alterar, sugiere que G27 202 desempeña poca o ninguna acción antireumática; se piensa, sin embargo, que este producto merece una seria consideración como agente terapéutico alternativo en la artritis reumatoide.

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TIETZE'S SYNDROME

BY

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Little has appeared about this condition in recent years in Great Britain, but our experience suggests that it may be more common than supposed, and may need to be considered in a differential diagnosis of chest pain.

Tietze (1921) described a condition of painful non-suppurative swelling of the costochondral or sternoclavicular joints. The following criteria should be met:

(1) Painful and tender enlargement in the region of one or more of the costosternal junctions;

(2) This enlargement should not have been present previously, and should regress without therapy.

Tietze found no other abnormal findings, and the condition was self-limiting and of unknown aetiology.

A revival of interest occurred at the beginning of the second world war, when Gill, Jones, and Pollak (1942) described the syndrome in five young soldiers. He noticed the persistence of the symptoms and absence of pathological changes.

Geddes (1945) observed a series of 35 cases in Canadian soldiers who were otherwise in good physical condition. Deane (1951) described seven cases, and Kayser (1956) was able to review 159 cases in the world literature, with special attention to 24 in which biopsies were taken.

The latest review is that of Karon, Achor, and Janes (1958), who reported their findings in six females and seven males, in whom the symptoms of swelling had persisted for from 3 days to more than 3 years.

Present Investigations

Three cases recently studied are described below:

Case 1, a previously fit but slightly obese male aged 25, complained of pain in the right anterior region of the chest for 2 months. This had followed an upper respiratory tract infection and unproductive cough. Shortly after this, he had noticed tender swellings over the right second, third, and fourth costosternal junctions. These had persisted despite local application of heat and a course of achromycin.

At this time the patient was in normal health apart from the swellings. The erythrocyte sedimentation rate was 54 mm./hr (Westergren), and the total white cell count 14,700/c.mm., with 43 per cent. lymphocytes. There was a pyrexia of 99·4° F. An oval, tender swelling, 3 in. by 2 in., was fixed to the deep structures over the second right costochondral junction, and these changes were found to a lesser degree over the third and fourth costosternal junctions. A diagnosis of Tietze's syndrome was made, but in view of a persistent slight pyrexia and raised erythrocyte sedimentation rate not previously found in this condition, a full series of investigations were carried out.

Laboratory Tests.—A chest radiograph and tomography of the costochondral junction showed no abnormality. The Wassermann reaction and Kahn test were negative. The blood cholesterol, uric acid, and electrolytes were normal. The agglutination tests for *Brucella abortus* and *B. melitensis*, typhoid, and paratyphoid showed no rise in the antibodies to these infections. The Paul Bunnell reaction was negative. There was no increase in the cold agglutinins. The Rose-Waaler test was negative, and the antistreptolysin titre was only 90 Todd units/c.mm.

Therapy.—Local pain and swelling persisted, and continued to be accompanied by a mild pyrexia with a raised erythrocyte sedimentation rate and lymphocytosis. Because of this, oral prednisolone 5 mg. three times daily was prescribed, and within 3 days there was a marked improvement, with disappearance of pain, diminution of the swelling, and a fall in the temperature and erythrocyte sedimentation rate.

Biopsy.—A biopsy of the third costal cartilage was taken through a transverse anterior chest incision. The surrounding soft tissue and perichondral tissue was oedematous. The costal cartilage appeared normal, but buckled readily on exposure nearest the junction with the

sternum. The cartilage was removed, together with some granulomatous tissue found beneath it. Microscopically the costal cartilage was normal, but in the surrounding soft tissue and ligament there was a chronic inflammatory round cell infiltration (Figs 1-4). There was no evidence of tuberculosis.

Figs 1-4.—Photomicrographs showing normal cartilage surrounded by tissue in which there is a chronic inflammatory round cell infiltration.

Fig. 1. × 20 Cartilage.

Fig. 3.

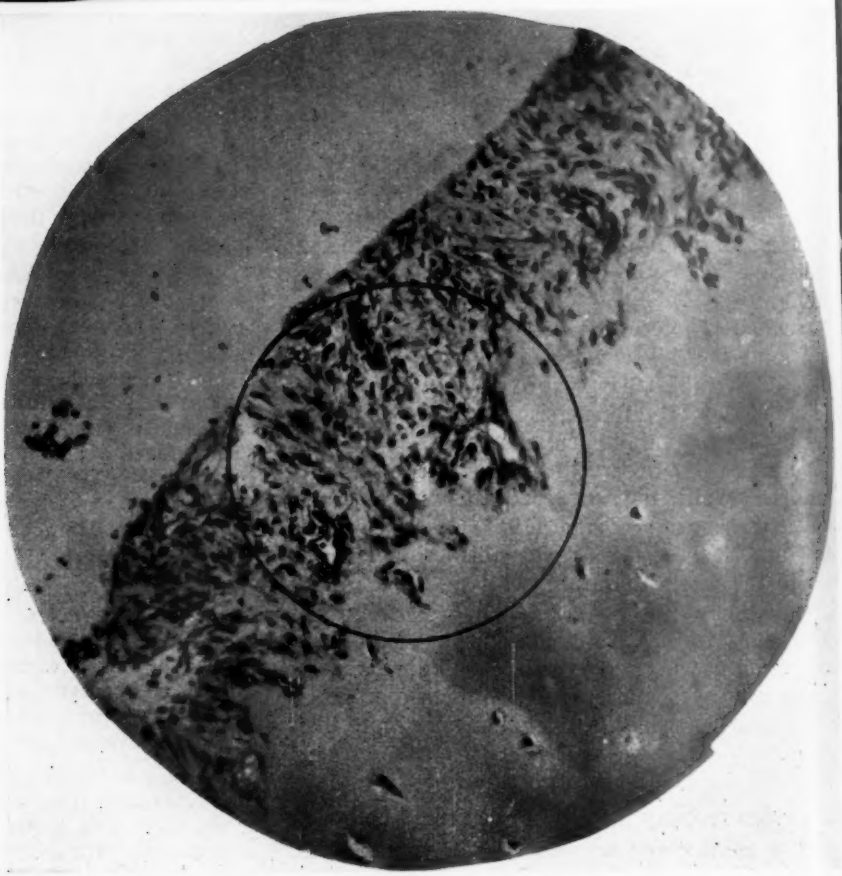

Fig. 2. × 120 Perichondrium.

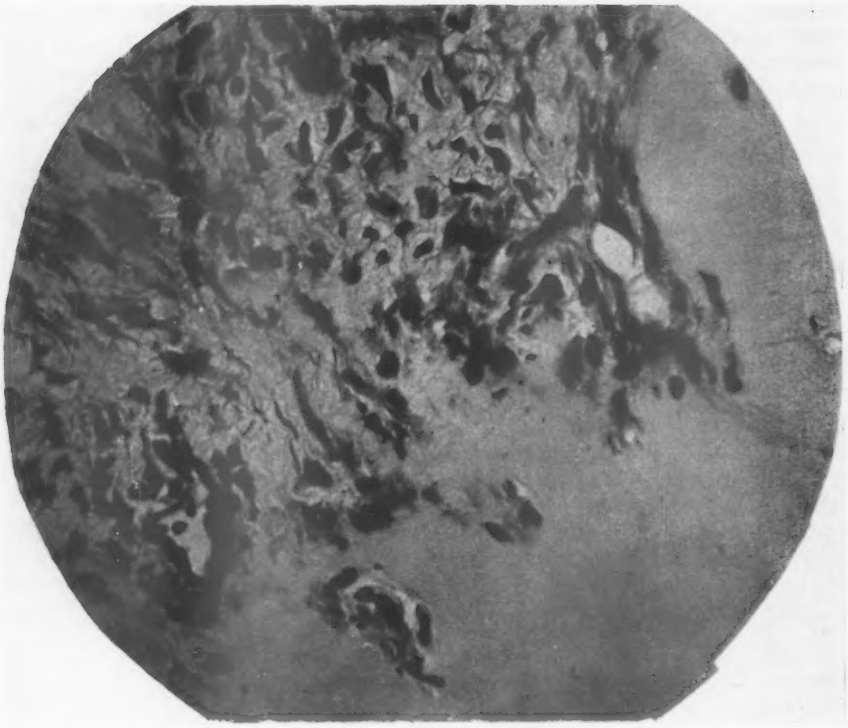

Fig. 3. × 300 Detail of Fig. 2.

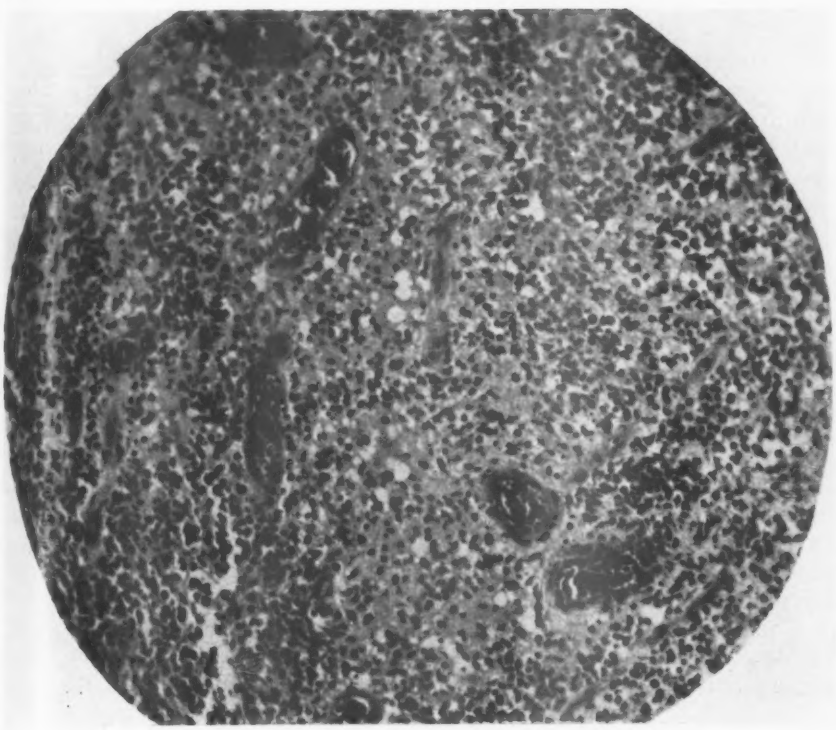

Fig. 4. × 120 Detached adjacent tissue showing inflammatory infiltration.

Result.—Recovery was rapid, and when seen 8 weeks later the patient had become symptom-free with no recurrence of the swelling; the erythrocyte sedimentation rate and differential white cell count were normal.

Case 2, an 18-year-old male, complained of occasional chest pain over a swelling that had appeared insidiously some 7 weeks previously with no antecedent illness or trauma. Examination showed no abnormality except for a small, palpable, tender swelling over the region of the second and third right costosternal junctions.

A radiograph of the chest was normal, and the haemoglobin estimation, white cell count, and erythrocyte sedimentation rate were normal. The patient said that the condition was improving, and 8 weeks later all signs and symptoms had completely cleared.

Case 3, a 50-year-old male, complained of right anterior chest pain of 2 months' duration. He attributed this to riding a frisky horse when not feeling well after an upper respiratory tract infection. The pain and tenderness had persisted, but had been considerably relieved by a course of radiant heat. A small, tender lump had been noticed, and he was anxious about it.

The patient had a mild generalized bronchospasm and there was a small, tender, smooth, fusiform lump over the second right costosternal junction; it was attached to deep structures, and was rubbery in consistency.

A radiograph of the chest was normal. The Wassermann reaction and Kahn test were negative. The Rose-Waaler and blood uric acid estimations were normal. The patient was given a further course of radiant heat, the swelling gradually subsided, and he has had no further trouble.

Discussion

Twenty cases reported in detail in the literature, and a further 47 occurring in series, have been studied, in addition to three reported above. It is likely that the syndrome is more common than would appear from the frequency of case reports. This may be due to unawareness of the diagnosis, but symptoms and signs are often trivial, and our second patient had not even mentioned his symptoms at his initial medical examination.

Pain is the most usual symptom. This is situated in the front of the chest, and occurs most commonly on the left side. It may be of acute or gradual onset, and may vary from a dull ache to a severe pain which is sometimes described as crushing or boring in nature. It may resemble pleuritic pain, and the time of day, posture, nature of work, and the existence of intercurrent illness may affect its severity. It may become worse on movement, or on increased respiratory excursion. This, if it accompanies exercise, may lead to confusion with anginal pain, but it is usually clearly differentiated by its persistent character.

The patient may also notice a lump. This usually lies over the sternoclavicular or costosternal joints on either side, as far down as the ninth rib. One or more swellings may occur, and they vary from about 1 cm. in diameter, to a fusiform swelling 10 cm. or more in length. There is no erythema of the overlying skin, which is usually tender on palpation. Kayser noted that in 69 per cent. of patients in his series only single swellings were present, whereas in the other 31 per cent. there were multiple swellings. Of 66 swellings, equal numbers were right- and left-sided, and the commonest site was the second costosternal junction. Considerable variation in the duration of the swelling has been noted. It may last for only a few days, or it may persist, varying in size, for over a year.

In most cases reported, the erythrocyte sedimentation rates and white blood cell counts were normal. Frey (1956) found that in four of his cases a lymphocytosis was present. Examination of the blood for the presence of cold agglutinins showed no abnormality. The blood chemistry was reported to be abnormal by de Haas (1952), in that the serum uric acid was 4-5 mg./100 ml. and the cholesterol was 300-400 mg./100 ml. This was not confirmed later, and Klages (1957) found no abnormality in the blood urea, total protein, fasting blood sugar, calcium uric acid, cholesterol, inorganic phosphorus, or the liver function tests. One of our three cases had a raised erythrocyte sedimentation rate and lymphocytosis.

Radiography of the chest is normal, though occasional deposits of calcium are noted; tomography of the affected area and electrocardiography, done when pain was the dominant symptom, have shown no abnormality.

The findings in biopsy specimens from 24 cases have been summarized by Kayser (1956). It is difficult to assess these findings, as in many cases the biopsy was limited to the costal cartilage itself, and did not include the surrounding soft tissues; in no case was the interarticular sternocostal ligament examined. No abnormality was found in six specimens examined. In the majority of specimens, the cartilage was normal microscopically and macroscopically. Five specimens were said to show swelling, pallor, or buckling. In three cases the cartilage was abnormal, chondroma, fibrotic change, and degeneration being reported. It is therefore possible, as Kayser suggested, that disease of the cartilage does not occur, and in our case it was normal. In seven specimens, abnormality of the surrounding soft tissues was found, varying from round-cell infiltration with thickening of the perichondrium to fibrosis.

No particular age or sex distribution has been noted. Cases have been reported in Western Europe, Japan, and in the United States, where it occurs in both the white and black races. It was first noted by Gill and others (1942), and later confirmed by Geddes (1945), that the syndrome is frequently preceded by respiratory infection, usually of the upper respiratory tract, but in some, by bronchitis or pneumonia. Thus Kayser (1956), in his review of the world literature, showed that 51 of 65 cases where a specific inquiry had been made had had a recent respiratory infection and that the other fourteen cases had not. Cough is a possible factor, but the swellings appear in some cases before the patient develops a cough and the marked unilateral occurrence in any individual would not seem to support this theory.

Whilst respiratory infection may be coincidental, it is interesting to speculate on the similar findings of Rose (1957) in the relationship of respiratory infection to polyarteritis nodosa. On the other hand, Düben (1952), in all the ten cases in his series, found no evidence of previous upper respiratory tract infection.

Tietze considered the condition to be a dystrophy of the cartilage, secondary to tuberculosis or malnutrition, although no change was found in the cartilage taken by biopsy from one of his cases. No evidence of tuberculosis has ever been shown, while malnutrition is unlikely because of the frequency of the syndrome in well-nourished young men in Geddes' series. Beck and Berkheiser (1954) thought that the interarticular sternocostal ligament contracted and caused a buckling of the cartilage. Motulsky and Rohn (1953) suggested that trauma of this ligament gave rise to a clinical picture analogous to a sprain in a peripheral joint. Bernreiter (1956) thought that trauma was the most likely cause. Buckling of the cartilage seems an improbable cause, as it has been reported in relatively few cases and may occur in normal people after retraction of the perichondrium for biopsy purposes. It is difficult to see how buckling of even a few relatively small costal cartilages could produce the marked swelling of 10 cm. length sometimes seen.

In our case, the swelling was due to round-cell infiltration and thickening of the surrounding soft tissue. The rapid response to local and systemic corticosteroids might suggest that a local disease of cartilage is present.

Diagnosis.—The recognition of this syndrome allows the early and complete reassurance of the patient. It has to be distinguished from diseases of the costal cartilage such as osteochondritis, chondroma, or malignant change in the cartilage or chest wall. The pain may have to be differentiated from that due to pulmonary or cardiac disease. The syndrome may occasionally simulate such miscellaneous conditions as Hodgkin's disease, multiple myelomata, syphilitic periostitis, presternal oedema of mumps, herpes zoster, rheumatoid arthritis affecting the second to fifth costosternal joints, typhoid, paratyphoid, and brucellosis. In women, this syndrome may give rise to considerable anxiety when it occurs beneath breast tissues, as it may appear to be a neoplasm.

Treatment.—This consists of local measures and reassurance. In mild cases, radiant heat is often sufficient. Procaine infiltration has been tried with temporary relief. Celio and Nigst (1956) reported the successful relief of pain with a local injection of 20-37·5 mg. hydrocortisone. Frey (1956) treated one patient with thyroid extract and obtained some improvement. In one of our patients with severe local symptoms and evidence of systemic upset, an excellent response was made to prednisolone in doses of 15 mg. daily for 7 days.

Summary

Three cases of Tietze's syndrome are reported, with the biopsy finding in one case.

The symptomatology in 67 cases from the literature and the pathological findings in 24 biopsies are discussed. It is concluded that the pathological changes occur not in the cartilage but in the soft tissues. The aetiology of the condition is unknown; its possible causation is discussed. Successful therapy with local and systemic corticosteroids is reported.

Our thanks are due to the D.G.M.S. (R.A.F.) for permission to publish this report, and to Wing-Cmdr. Cross and the staff of the R.A.F. Institute of Pathology and Tropical Medicine who provided the photomicrographs.

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Syndrome de Tietze

RÉSUMÉ

On relate trois cas de syndrome de Tietze, y compris le résultat de la biopsie dans un cas.

On discute la symptômatologie dans 67 cas trouvés dans la littérature et les résultats anatomo-pathologiques des 24 biopsies. On conclut que les altérations anatomo-pathologiques surviennent non pas dans le cartilage mais dans le tissu mou. L'étiologie de cette affection n'est pas connue; on en discute les causes probables. On relate le succès du traitement corticostéroide, local et général.

Síndrome de Tietze

SUMARIO

Se relatan tres casos de síndrome de Tietze, incluyendo el resultado de la biopsia en un caso.

Se discute la sintomatologia en 67 casos encontrados en la literatura y los resultados anatomo-patológicos de 24 biopsias. Se concluye que las alteraciones anatomo-patológicas no ocurren en el cartílago, sino en el tejido blando. La etiología de esta afección se desconoce; se discuten sus causas probables. Se relata el éxito terapéutico con corticosteroides locales y generales.

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NUCLEOPROTEIN-LATEX AGGLUTINATION TEST IN CONNECTIVE TISSUE DISEASES*†

BY

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Research into the aetiology of the collagen diseases has been guided recently by the speculation that they may be manifestations of hypersensitivity. Rheumatoid arthritis and disseminated lupus erythamatosus especially, it has been suggested, could be the results of "auto-immune" processes. The work of Klemperer, Gueft, Lee, Leuchtenberger, and Pollister (1950) focused attention on the role of deoxyribosenucleic acid in disseminated lupus erythematosus. Subsequently, Miescher and Strässle (1957) described deoxyribosenucleic acid antibodies in the disease. These investigators used haem-agglutination of sensitized sheep red cells to estimate antibody titres, but suggested that latex particles might also be used. Christian, Mendez-Bryan, and Larson (1958) recently described the use of latex particles sensitized with nucleoprotein as a test for disseminated lupus erythematosus. This report describes our results with a nucleoprotein-latex agglutination test on the sera of patients with lupus, rheumatoid arthritis, and certain other diseases. We also performed F II haemagglutination tests (method of Jacobson, Kammerer, Wolf, Epstein, and Heller, 1956) on most of these sera.

Materials and Methods

(1) Deoxyribosenucleoprotein was obtained by the standard method (Zamenhof, 1957) of washing a homogenate of calf thymus in 0·1 molar sodium citrate and subsequently extracting the nucleoprotein with 1 molar sodium chloride. The nucleoprotein was precipitated twice by making the solution 70 per cent. with respect to ethyl alcohol, and the nucleoprotein fibres finally dissolved in 1 molar saline. The nucleoprotein from 50 g. calf thymus was dissolved in 100 ml. molar saline, and had a nitrogen/phosphorus ratio of 331/96. The nucleoprotein was stored frozen, and retained its activity for at least 5 months.

(2) The nucleoprotein-latex agglutination test was performed as follows: Polystyrene latex of particle size 0·81 micra was diluted with distilled water so that the final light transmission of a 1 per cent. solution was 5 per cent. in a spectrophotometer at 650 millimicra with a red filter. The final test solution contained 1 per cent. of this latex suspension, 1 per cent. of the nucleoprotein solution, and 98 per cent. of glycine-saline buffer pH 8·2.

Serial doubling dilutions of the test sera were made in the range of 1 : 2 to 1 : 4096, using the pH 8·2 buffer as diluent. To each dilution was added an equal volume (0·25 ml.) of nucleoprotein-latex suspension. The tubes were incubated at 37° C. for 2 hrs, then centrifuged for 3 mins. at 1,750 r.p.m. The resulting agglutination was read and graded 1 plus (+) to 4 plus (++++). Agglutination in any dilution greater than 1 plus was regarded as positive.

We did not centrifuge and wash the sensitized latex particles as did Christian and others (1958); we found this arduous manœuvre unnecessary. Any nucleoprotein fibres which form may be lifted out before the sensitized latex suspension is added to the serum dilutions. Our titres are comparable to those reported by Christian and others (1958), who washed the sensitized latex several times.

(3) Any serum causing agglutination was tested against unsensitized latex particles. For a positive test at least a twofold dilution difference was required between the agglutination in the sensitized and unsensitized latex particle system.

(4) L.E. cell preparations were made by mixing four drops of the buffy layer of heparinized blood with six drops of the serum under test. The temperature of all reagents and glassware was kept at 37° C. The mixture was incubated for 2 hrs at this temperature, then gently centrifuged. A smear was made of the sediment. Each

* This study was supported in part by a grant (A-1229) from the National Institutes of Health, Arthritis and Metabolic Diseases, and by a grant from Geigy Pharmaceuticals, Yonkers, New York.

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‡ Trainee of the National Institutes of Health, United States Public Health Service.

slide was examined for at least 15 min. before being pronounced negative.

(5) Sera for testing were obtained as follows:

(*a*) Rheumatoid sera were derived from specimens sent to this laboratory for routine F II haemagglutination tests.

(*b*) Sera were obtained from patients with disseminated lupus seen at this hospital over the past 2 years. Sera from similar patients were also donated by colleagues in private practice.

(*c*) Sera of patients with discoid lupus were obtained from the Dermatology Clinic.

(*d*) "Normal" sera consisted of those received by the blood bank for typing. They were, therefore, both from normal persons and from patients with miscellaneous diseases.

(6) F II haemagglutination tests were performed by the standard technique (Jacobson and others, 1956).

Results

The results of tests with latex sensitized with nucleoprotein are shown in the Table. Titres ranging from 1 : 2 to 1 : 4096 were obtained using latex particles sensitized with nucleoprotein.

(1) Of 159 "normal" sera, three (1·9 per cent.) were positive. One (from a patient with spinal cord meningioma) had a titre of only 1 : 2, the other two had titres of 1 : 16 (a case of infectious hepatitis) and 1 : 256 (a case of Ehlers-Danlos syndrome). None of these three sera produced L.E. cells.

(2) Of sera from ten patients who had chronic discoid lupus, none caused latex agglutination or produced L.E. cells.

(3) Of 37 sera from patients with disseminated lupus erythematosus, 25 (68 per cent.) had positive latex tests in a titre ranging from 1 : 2 to 1 : 1024; 26 (70 per cent.) of the 37 sera produced L.E. cells, and 22 (88 per cent.) of the 25 with positive latex tests gave a positive L.E. cell reaction. Of the twelve disseminated lupus erythematosus sera which did not agglutinate latex, four produced L.E. cells. Of the 25 disseminated lupus erythematosus sera which agglutinated latex, thirteen (52 per cent.) had positive F II haemagglutination tests. The percentage of the total group of disseminated lupus erythematosus sera which gave positive F II haemagglutination tests cannot be given since sufficient serum was not available in every case for testing. There was no correlation between the level of the nucleoprotein latex titre and the level of the F II titre.

(4) In rheumatoid arthritis, 33 (22 per cent.) of a total of 150 sera were positive. Among the 150 sera were ten from patients considered to be in the phase of rheumatoid arthritis which is accompanied by widespread arteritis and is characterized especially by neurovascular lesions. Only two of these ten sera were positive (titres of 1 : 4 and 1 : 16); neither produced L.E. cells. Only one of these ten sera produced L.E. cells, and this one gave a negative nucleoprotein-latex test. Two of the remaining 31 positive rheumatoid sera produced L.E. cells. The nucleoprotein-latex titre of these two was 1 : 16 and 1 : 1024, and the corresponding F II haemagglutination titres were >1 : 56,000 and 1 : 56,000 respectively. There was no apparent relationship between the F II haemagglutination titre and nucleoprotein-latex titre in either the lupus or the rheumatoid sera.

(5) In a group of eighteen sera, all positive in either or both the Kolmer and Kahn tests, seven were positive in the nucleoprotein-latex test in titres ranging from 1 : 2 to 1 : 32. Three of the seven had unquestionable syphilis, having either taboparesis or aortic aneurysms. Examination of the

TABLE

COMPARISON OF RESULTS OF NUCLEOPROTEIN-LATEX AND L.E. CELL TESTS

Results of Tests		Latex / L.E. Cell	Positive / Positive	Positive / Negative	Negative / Positive	Negative / Negative	Total No. of Tests
Types of Sera	"Normal"		0	3	0	156	159
	Lupus Erythematosus	Chronic discoid	0	0	0	10	10
		Disseminated	22	3	4	8	37
	Rheumatoid Arthritis	Without arteritis	2	31	0	107	140
		With arteritis	0	2	1	7	10
	Showing Positive Tests for Syphilis		1	6	0	11	18

records of the other four leads one to suspect that they may have had biologic false positive tests for syphilis. Unfortunately, the results of *Treponema pallidum* immobilization tests are not available. One of these seven sera produced classical L.E. cells. The record revealed that this serum was from a 45-year-old coloured female who had had chronic uveitis for 6 months. We think it likely that this patient will eventually develop signs of disseminated lupus erythematosus.

Discussion

Our results confirm the usefulness of a nucleoprotein-latex test in disseminated lupus erythematosus, since the sera from 68 per cent. of such patients in our series gave a positive result. The test is much easier to perform than the classical L.E. cell test and, in addition, allows for some quantitation of the amount of "lupus factor" present. The occurrence of positive tests in diseases other than disseminated lupus erythematosus may mean that the test is sufficiently sensitive to detect small amounts of the "lupus factor", or a related substance, in those diseases.

The results of the test in rheumatoid arthritis confirm again the well-known fact that "lupus factor" is found in about 20 to 25 per cent. of patients with that disease (Friedman, Sickley, Poske, Black, Bronsky, Hartz, Feldhake, Reeder, and Katz, 1957). It has been known for some years that the sera of many patients with disseminated lupus erythematosus give a positive reaction in serological tests for syphilis. Miller, Slatkin, Brodey, Wechsler, and Hill (1957) reported that serological tests for syphilis were positive in eleven of fourteen cases of acute disseminated lupus erythematosus with L.E. cells. Moore and Mohr (1952) stated that there was a 20 per cent. incidence of biologic false positive tests for syphilis in lupus erythematosus. It is of interest that seven of the eighteen sera in our series which were positive for syphilis also were positive in the nucleoprotein-latex test. At least one of these seven patients has probable lupus, three have undoubted syphilis, and three are probably biologic false positives. It is, of course, not known exactly what is being titrated in the nucleoprotein-latex test; there is a strong suspicion that nucleoprotein antibodies are being measured, especially since preliminary studies in our laboratories show that rabbits immunized with nucleoprotein injections produce serum which strongly agglutinates the test system. However, the fact that undoubted syphilitic sera agglutinate the latex suggests that something other than nucleoprotein antibodies may be involved.

Dameshek (1958) recently postulated that disseminated lupus erythematosus may be a complex of auto-immune abnormalities involving various constituents of the blood and endothelial surfaces. Our results confirm that, whatever initiates the disturbance in disseminated lupus erythematosus, the resulting immunological abnormalities are multiple and include nucleoprotein antibodies as well as the antibodies found in syphilis. The important question of which factor or factors are primary remains unanswered. It would seem most unlikely that nucleoprotein antibodies alone are primary, since Bardawil, Toy, Galins, and Bayles (1958) have shown, and we have confirmed in our laboratory, that high circulating levels of nucleoprotein antibodies in animals do not lead to the production of the histological lesions of lupus in these animals.

Summary

The usefulness of a nucleoprotein-latex test in the diagnosis of lupus erythematosus has been confirmed. The test was positive in 68 per cent. of patients with disseminated lupus erythematosus, in 22 per cent. of patients with rheumatoid arthritis, and in only 1·9 per cent. of patients with other diseases excluding syphilis. In sera giving positive tests for syphilis, 39 per cent. were positive. In disseminated lupus erythematosus the test correlated well with the L.E. cell test.

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Réaction d'agglutination nucléoprotéine-latex dans les maladies du tissu conjonctif

RÉSUMÉ

On a confirmé l'importance de la réaction nucléoprotéine-latex dans le diagnostic du lupus érythémateux. Cette réaction était positive dans 68% des cas de lupus érythémateux disséminé, dans 22% des cas d'arthrite rhumatismale et seulement dans 1,9% des malades atteints d'autres maladies, sauf la syphilis. Parmi les sérums donnant une réaction syphilitique positive, notre réaction était positive dans 39% des cas. Dans le lupus érythémateux disséminé il y avait une bonne corrélation entre cette réaction et le phénomène L.E.

Reacción de aglutinación de nucleoproteína-latex en las enfermedades del tejido conjuntivo

SUMARIO

Se confirmó la importancia de la reacción de nucleoproteína-latex para el diagnóstico del lupus eritematoso. Esta reacción fué positiva en el 68% de los casos de lupus eritematoso diseminado, en el 22% de los casos de artritis reumatoide y sólo en un 1,9% de casos con otras enfermedades, excepto la sífilis. Para sueros con reacción sifilítica positiva, nuestra reacción dió una reacción positiva en un 39% de los casos. En el lupus eritematoso diseminado hubo una buena correlación entre esta reacción y el fenómeno L.E.

Ann. rheum. Dis. (1959), **18**, 259.

HEBERDEN SOCIETY

A joint meeting of the Heberden Society and the British Association of Physical Medicine was held at Buxton on July 25 and 26, 1959, to celebrate the Centenary of the Devonshire Royal Hospital.

Demonstrations

DR. J. H. BLAND, DR. F. D. GRAY, and PROF. J. H. KELLGREN (*Manchester*) presented an exhibition illustrating a review of 29 patients considered in 1950 to have generalized osteo-arthritis. This series will form the subject of a paper to be published in a future issue of the *Annals*.

MR. J. H. CREGAN (*Buxton*) presented a patient with rheumatoid arthritis complicated by cervical subluxation and paraplegia.

DR. R. HARRIS (*Buxton*) exhibited studies on the circulation of joints, using ^{23}Na Sodium chloride.

MR. J. CHARNLEY (*Manchester*) demonstrated fluon ("Teflon") prostheses for use in arthroplasty of the hip.

Papers.—The following papers were read by members of the Heberden Society and guest speakers:

DR. N. CARDOE (*London*): **A Controlled Trial of G27 202 in Rheumatoid Arthritis.** This paper and the discussion thereon appears on page 244 of this issue of the *Annals*.

DR. R. K. W. KUIPERS (*The Hague*): **Adrenal Steroids in Combination with Pyrazolones in the Treatment of Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis, and Ankylosing Spondylitis.** These drugs were among the most common forms of treatment for rheumatoid arthritis, juvenile rheumatoid arthritis, and ankylosing spondylitis. As a result of its experiences his group had, from an early date, stressed the need to keep dosage as low as possible, controlling phenylbutazone treatment by estimation of blood levels, and controlling the adrenal atrophy of continued steroid treatment by regular doses of corticotrophin. With a view to further reductions in dosage he had investigated the possibilities of combined therapy with prednisone and phenylbutazone, given as compound tablets called "Deltabutazolidin" containing 1·25 and 50 mg. of these drugs respectively. An initial dosage of six such tablets a day was usually satisfactory and could often be reduced to three a day.

Gsell and Rechenberg (1953) had announced that, in twenty cases, after "boost" therapy with cortisone, they maintained good results with phenylbutazone. Dr. Kuipers' trials of this combined therapy had been conducted in two parts:

(1) A "non-placebo-controlled", but carefully assessed trial in 300 patients with rheumatoid arthritis, eight with juvenile rheumatoid arthritis, and fifty with ankylosing spondylitis;
(2) A "double-blind placebo-controlled" trial of tablets randomly allocated to 100 patients with rheumatoid arthritis.

Besides Deltabutazolidin or a placebo, both groups received 0·75 g. aspirin and 0·75 g. phenacetin daily. Prednisone had not been found to influence the excretion rate or blood levels of phenylbutazone. On the other hand, there was evidence from the investigations of Kersten and Staudinger (1957) and Korus, Schriefers, and Dirscherl (1956), that phenylbutazone might inhibit the inactivation of prednisone.

The results in the first (non-comparative) trial were very good, all but eight of the rheumatoid patients, including two who might have had co-existing systemic lupus erythematosus, received some benefit and none became worse. Comparatively large doses (in relation to body weight) were required to maintain improvement in children.

These good results were confirmed by the second (controlled) trial. Assessments were made according to the grades and criteria of the American Rheumatism Association (Steinbrocker, Traeger, and Batterman, 1949). Toxic side-effects were negligible; only one gastro-intestinal upset occurred (in a patient known to be liable to this) and oedema of the ankles appeared in six patients, but was controlled by interruption of treatment. The blood pictures remained within normal limits, and four patients who had previously developed skin reactions during or after treatment with phenylbutazone showed no such reactions during treatment with Deltabutazolidin.

Dr. Kuipers concluded that it was possible, as a result of treatment with Deltabutazolidin in a dosage of four to six tablets daily, to bring the rheumatic process to a quiescent phase without undesirable side-effects. He then described the use of measurements of urinary polysaccharide output (according to the method of Di Ferrante and Rich, 1956) in the objective assessment of rheumatoid arthritis. They had found the normal output for adult men was 4·8 mg. per 24 hrs (range

2·1 to 6·9) and for women 3·7 mg. per 24 hrs (range 1·8 to 5·6), higher figures being found in children. High outputs in patients with active rheumatic disease were reduced in parallel with the clinical findings after successful treatment. Using this test, there was some evidence that the compound Deltabutazolidin tablet was more effective than comparable amounts of its individual constituents.

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Discussion.—PROF. E. G. L. BYWATERS (*Taplow*) said that Dr. G. Loewi had been studying the urinary polysaccharide output in patients at Taplow. There was great variation from person to person, and whilst salicylates might decrease the output in some patients, it appeared to increase it in others. He felt that it was premature to use this test as an objective measure of disease activity. He also wondered if it was not a retrograde step to use a compound tablet instead of the individual constituents. It implied an unvarying ratio of dosage which might not accord with the varying needs of each patient.

DR. KUIPERS replied that with his method, which enabled him to estimate the 24-hr urinary mucopolysaccharide output in series with a constant pH, no great variations had been noted. At the beginning it was found that a wrong and inconstant pH during the estimations gave rise to variations. The method was to be described in the thesis of one of his collaborators.

DR. M. F. MCMAHON (*Cork*) said that he had tried Deltabutazolidin in 125 patients in the last 9 months. He thought it was "the best remedy we had yet". It appeared to be free from toxicity and, of fifty patients switched to it from phenylbutazone (without their knowledge), most felt and fared better.

MR. J. CHARNLEY (*Manchester*): **Experimental Observations on the Lubrication of the Joints.** This paper and the discussion thereon will appear in the next issue of the *Annals*.

DR. J. J. DE BLÉCOURT (*Groningen*): **Mobile Physiotherapy in the Netherlands.** A special number of the *British Journal of Physical Medicine* had reported 3 years ago that home physiotherapy services, mostly voluntary, were reaching people who were unable to attend a hospital physiotherapy department in the towns and rural areas of Britain.

Many patients deteriorated quickly without physiotherapy, especially whilst awaiting a hospital vacancy or after discharge from hospital. In some of these the tragic consequences of inactivity could be averted by home physiotherapy. Patients with locomotor disorders were especially in need of such care. In the Netherlands doctors were keen to explore all means of fighting rheumatism, but their efforts had been limited by lack of facilities for the diagnosis and treatment of the large number of patients with chronic rheumatism. They were striving to found a number of centres for rheumatic diseases, attached to Universities or to teaching hospitals, and comprehensive home care (involving the co-operative efforts of general practitioner, nurse, almoner, and physiotherapist) was also becoming as an important part of the service, particularly in rural areas.

Before initiating such a service, Dr. de Blécourt had visited England, but had been disappointed to find only one doctor (a general practitioner near London) who had been at all enthusiastic about mobile physiotherapy, and several specialists in rheumatic diseases had been either not interested or positively against the idea. Most thought that no good could come of treatment not supervised by a specialist, and that proper physiotherapy could only be given in a specially organized department; anything less was considered a waste of time and money. Mobile physiotherapy, as seen at work in England, obviously reflected this lack of interest. It was insufficiently supervised, too much palliative treatment was given, and only a small part of the equipment available was in regular use. Despite this discouragement, a suitably organized mobile physiotherapy service seemed to have good possibilities, and such a service had been started in some areas of the Netherlands. A mobile unit consisted of a Ford van or Volkswagen with infra-red or radiant heat apparatus, wax baths, slings for exercising arms and legs, crutches, medical balls, and so on. There was no shortwave, ultra-violet, or other complicated apparatus. It was staffed by experienced and specially trained physiotherapists (male or female), under the guidance of a medical director. Any general practitioner or specialist could call on the services of the mobile unit in his area, and each request was assessed by the medical director by several established criteria, including inavailability of a private physiotherapist and inability of the patient to leave home. Hitherto this service had been used only for rheumatic patients.

In 1958 the mobile physiotherapy unit at Groningen had treated 53 patients with about twenty treatments per patient, and about 15½ miles had been travelled per treatment. The cost was about £1,200 and the fees received about £600. Sickness insurance funds paid the normal fee plus a contribution for travelling expenses. Private patients paid for themselves. The Netherlands Rheumatic Association met the deficit from public subscription without Government aid. Building contractors had given over £6,000 for this purpose. Four mobile units were already in operation and others were planned.

The results had been very satisfactory. Treatment was given usually twice weekly for 6 weeks, and then once weekly for up to 2 months. The physiotherapist-in-charge regularly consulted the medical director as well as the general practitioner and district nurse in the patient's home area, in-patients being interviewed before discharge from hospital. It had often been possible to shorten the duration of stay in hospital or to prevent the patient from losing the gains made in hospital, and sometimes hospital admissions could be avoided by the use of the mobile unit.

The best results had been seen in cases of ankylosing spondylitis, rheumatoid arthritis, and periarthritis of the shoulder, the results in the cases of osteo-arthritis

being not so good. The service had awakened much public interest and its help had also been sought for patients with non-rheumatic conditions such as poliomyelitis.

Mobile physiotherapy could be of real help to patients, and could play a very useful part in treatment. Careful medical supervision was, of course, a necessity, and without it the mobile physiotherapy service was doomed to fail.

Discussion.—DR. C. B. HEALD (*Royal Free Hospital. London*), who had originated the idea of mobile physiotherapy units in England, commented that such units had proved, in practice, to have certain drawbacks:

(1) Low turnover, usually less than nine patients treated per physiotherapist per day;
(2) A tendency for the cases treated to be of the aged hemiplegic type;
(3) Loss of the stimulus and group optimism inherent in a good physical medicine centre;
(4) A tendency to keep up repetitive passive placebo treatments;
(5) The resulting high cost in money and personnel.

Realizing the force of these drawbacks and the urgent need for reaching rural areas with good rehabilitation, he had devised and worked out, with Morris Motors, a well-equipped Physical Medicine Department. This was based on the known experience of mobile *x*-ray departments and dental surgeries, and the Slough Mobile Surgery.

This scheme, he affirmed, had the following advantages in comparison with existing mobile physiotherapy units:

(1) High turnover, comparing favourably with average Hospital Departments.
(2) Predominance of full-recovery cases.
(3) Group recovery stimulus provided by the unit waiting-room and village-green location.
(4) Possible saving in total cost by relief of the ambulance service.

DR. C. R. L'ESTRANGE ORME (*Parkstone, Dorset*) had had experience of a mobile physiotherapy unit in the remote parts of Dorset. In some villages there might be only one patient to treat and he might as well be treated in his home as in a mobile department. If fit enough, such a patient should be brought to the active atmosphere of a hospital department. There was a psychological difficulty in discontinuing home therapy in many cases and such a service offered great scope for waste of valuable effort.

DR. L. J. BARFORD (*Redhill*) said that he had been associated with a mobile physiotherapy unit for 10 years. It consisted of two vans and two physiotherapists. It ran at a loss of £1,200 a year and had to be helped by other means. He would agree with Dr. Heald that its use did not come up to expectation and that much time could be wasted in giving long courses of ineffectual treatment.

DR. F. S. COOKSEY (*Dulwich*) thought that it was better to treat patients in hospital and to send the physiotherapist once or twice to their houses to make sure they were continuing satisfactorily rather than to attempt treatment.

DR. R. HARRIS (*Buxton*) felt that a little physiotherapy was of no value. If a rheumatic patient needed treatment then he needed short courses of carefully planned active treatment, not long-drawn-out occasional passive treatment.

PROF. KELLGREN said that there were disadvantages in the use of Mobile Physiotherapy Units especially in England, but that the way in which they were used in the Netherlands (with strict criteria, careful medical supervision, etc.) seemed to open possibilities and to suggest that it would be useful to study the problem further.

DR. J. NORRIE SWANSON (*Toronto*): **New Techniques of Splint-Making.** "Durafoam" was a new plastic material, which made ideal supportive splints for arthritic patients. Two chemicals were mixed together and then poured into a plastic envelope, on the surface of which had been drawn the design of the splint. After a few minutes, the chemicals were hard enough for the design to be cut out. The preformed splint was then applied to the body, and maintained in position with a bandage. It finally hardened a few minutes later. The final product was a light, strong, comfortable splint. It could be lined with foam plastic, coloured by incorporating pigments, and remoulded by heat, and it was also buoyant, washable, and transparent to *x* rays. Successive remouldings allowed the gradual straightening of flexed joints in stages, still using the same splint. The strength of the plastic (which had a cellular consistency) allowed it to be used for many other gadgets and appliances.

Discussion.—In answer to various questions, Dr. Swanson said that the new material cost slightly more than the proprietary plaster-of-Paris bandages and would soon be available in Great Britain. Since it could be used over and over again and there were fewer overheads, it was probably more economical than plaster in the long run. It was non-sensitizing and non-toxic.

DR. HARRIS (*Buxton*) mentioned experiments with nylon-impregnated plaster-of-Paris for wrist supports. This substance was rather slow to harden, but was washable and could be worn by patients undergoing hydrotherapy.

DR. SWANSON later demonstrated the making of a Duraform splint.

DR. W. R. M. ALEXANDER and DR. J. J. R. DUTHIE (*Edinburgh*): **Studies of the Anti-Nuclear Factor in Disseminated Lupus Erythematosus.** Friou (1957) had reported that serum from patients suffering from disseminated lupus erythematosus (L.E.) contained a factor with an affinity for nuclei of tissue cells. His original observations had been amply confirmed by other workers, and the anti-nuclear factor (A.N.F.) had been characterized as a gamma-globulin.

Like the L.E.-cell phenomenon, A.N.F. had so far been demonstrated only *in vitro* and there was no evidence that nuclei of living cells were capable of reacting with it.

A.N.F. was detected by the fluorescent antibody technique of Coons (1950) which, in this application, was used as follows:

An unfixed blood film or other source of leucocytes was exposed to the serum under test for 30 minutes at room temperature and, if A.N.F. was present, it combined with the nucleus of the cell. At this stage no visible change in the cell could be demonstrated. Excess serum was washed from the slide which was then exposed for 30 minutes to rabbit serum containing antibody to human globulin. This serum had previously been conjugated, by chemical means, to a fluorescent dye.

If A.N.F. was present on the nucleus it bound the fluorescent antibody and the complex could be detected in the fluorescence microscope.

This indirect, or sandwich, technique was convenient in that only one serum had to be conjugated for screening large numbers of sera for A.N.F.

It was wished, however, to study the properties of A.N.F. in a few sera and for this purpose direct conjugation of test serum and fluorochrome was more satisfactory. The film was exposed to the direct conjugate and examined as before.

The experiments Dr. Alexander described were planned to examine the possible effect of A.N.F. on leucocytes in suspension and its relationship to the L.E.-cell phenomenon. Leucocytes were prepared from heparinized blood by differential sedimentation. The plasma was removed and replaced by conjugated serum known to contain A.N.F. and to exhibit the L.E.-cell phenomenon. Cells and conjugates were incubated at 37° C. for 2 hrs, and smears were then made. When dry, the slides were washed to remove excess serum and thereafter examined by phase contrast and fluorescence microscopy. Six individual conjugates were tested and leucocytes from healthy donors and patients suffering from disseminated lupus erythematosus were used. The results were the same in all experiments. L.E. cells were present and the inclusion bodies alone were fluorescent. There was no nuclear fluorescence of intact leucocytes or L.E. cells.

These experiments showed that A.N.F. was not bound by intact leucocytes in suspension. At some point, the nuclei of cells destined to be phagocytosed must have combined with A.N.F., but whether this occurred before or after disruption could not be said. The experiments also illustrated that leucocytes in suspension—mainly living cells—differed from dead leucocytes in air-dried blood films in their reaction with A.N.F.

The effect of exposing damaged leucocytes in suspension to conjugated sera was next investigated. Damage was produced by exposure to ultra-violet light—a technique which did not cause morphological changes in the cells. Leucocytes from a healthy donor were irradiated in suspension in the donor plasma. Conjugated serum containing A.N.F. was then substituted for the plasma and incubation continued for 2 hrs. No L.E. cells were found—presumably because irradiation had rendered the cells incapable of phagocytosis—but, perhaps more surprising, nuclear fluorescence was not detected. Thus, although the cells were damaged, their nuclei did not bind A.N.F.

Preparations of leucocytes from patients suffering from disseminated lupus were similarly treated. In most experiments the results were the same as those obtained with irradiated leucocytes from healthy donors, but on two occasions a striking difference was observed. L.E. cells were found in the preparations and there was fluorescence of inclusion bodies in L.E. cells and of nuclei both of intact leucocytes and L.E. cells.

At first sight it was difficult to reconcile this result with those of the previous experiments. How might a leucocyte sufficiently damaged to combine with A.N.F. yet be capable of phagocytosing other nuclear material to form an L.E. cell? The answer, it was thought, was that these L.E. cells were formed before the leucocytes were exposed to the fluorescent sera. It had since been demonstrated that L.E. cells could indeed have been formed in the 30 minutes during which the leucocytes were being separated from the donor plasma. The subsequent uptake of fluorescent A.N.F. might be explained by postulating that the leucocytes, including the preformed L.E. cells, suffered some further change during their exposure to ultra-violet light in the presence of plasma containing A.N.F.

If this hypothesis could be substantiated it would imply that, in certain circumstances, damage to living cells in the presence of A.N.F. might be followed by uptake of A.N.F. If this could be demonstrated *in vivo*—and experiments had been begun to determine this—it would raise the status of A.N.F. from that of a serological oddity to a substance of possible importance in the pathogenesis of disease.

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Discussion.—PROF. E. G. L. BYWATERS asked if irradiation could destroy complement which was said to be necessary for phagocytosis.

DR. H. A. VALKENBERG (*Leyden*) agreed that complement was necessary for phagocytosis.

DR. ALEXANDER replied that he had not tested the effect of ultra-violet irradiation on complement, but that he had a strong suspicion that complement was unlikely to survive the process of conjugation.

PROF. J. H. KELLGREN (*Manchester*): **Report of the Joint Committee of the Empire Rheumatism Council and Nuffield Foundation. Prednisolone Analgesics Trial.** This report and the discussion thereon appears on page 173 of this number of the *Annals*.

DR. A. ST. J. DIXON and DR. H. DUNCAN (*Postgraduate Medical School, London*): **Familial Hyperuricaemic Nephropathy.** A young man of 19, investigated for high blood pressure and arthritis, had been found to have gout and severe renal disease. The serum urea was 106 mg. per cent. and the uric acid 19 mg. per cent. The question whether the gout was secondary to renal failure to excrete urates, or whether this was a severe example of gouty kidney, was investigated by examining the patient's family. Some 20 per cent. or more of first-degree relatives of a patient with gout should have a high serum uric acid, but this finding would hardly be expected in the family of a patient with primary renal disease. The family study disclosed that all the boy's five surviving siblings and both his parents were hyperuricaemic. This was strong evidence that gouty hyperuricaemia was the primary defect, passed with 100 per cent. penetrance from parents to offspring. However, it was also disclosed that all but two members of the family (including a sister who had died) showed some degree of renal disease, and none of the others had

gouty arthritis, although one subsequently developed it. The sister who had died had had chronic pyelonephritis clinically, and a review of the histology of the kidneys showed some features suggestive of gout. The mother and the remaining two sisters had all had "pre-eclamptic toxaemia" and had been left with evidence of residual renal damage. Two other brothers were well, but had raised blood urea, and one had albuminuria. The father and youngest brother had no evidence of renal disease—so far.

Thus, in this family hyperuricaemia existed without renal disease, but renal disease did not exist without hyperuricaemia, and it therefore appeared that hyperuricaemia was the primary defect and renal disease the complication. Dr. Dixon had called this condition "hyperuricaemic nephropathy" and had gone on to examine other causes of hyperuricaemia to see if similar renal damage could occur.

One difficulty was the diversity of renal lesions known to accompany primary gout. Nevertheless, the association with gout was common and rose with duration of disease to 100 per cent. in an autopsy series. Experimental urate infusions both in man and in animals, were directly damaging to the kidneys. Renal damage could complicate secondary gout: examples had been seen in chronic leukaemia, polycythaemia, congenital haemolytic anaemia, and myelomatosis. It also occurred in acute and chronic leukaemia and myelomatosis with hyperuricaemia but without gout. In an attempt to find out whether unsuspected hyperuricaemic nephropathy was the cause of otherwise unexplained hypertension, Dr. Duncan and Dr. Colin Dollery had studied about 100 patients attending a hypertension clinic. A large number were found to have hyperuricaemia, but this proved to be the result of the antihypertensive drugs in use. All these drugs, including chlorothiazide (and also pempidine and reserpine, not previously known to have this effect) could raise the serum uric acid without raising the blood urea.

In summary, it seemed possible that hyperuricaemia might damage the kidneys, and the concept of a hyperuricaemic nephropathy (either inherited or acquired) may explain the liability to renal disease of patients with both primary and secondary gout, and may also explain some of the renal disorders associated with blood diseases and myelomatosis. There was also a possibility that an inherited hyperuricaemia might in some patients cause otherwise unexplained renal disease, hypertension, toxaemia of pregnancy, or even symptomless albuminuria. These considerations had ceased to be of merely academic importance since potent uricosuric drugs were available to attack the underlying metabolic abnormality.

Discussion.—Dr. G. D. Kersley (*Bath*) asked about the effects of the uricosuric drugs on renal function in this case. He had had three cases of gout with renal disease who showed improvement in renal function with uricosuric drugs.

Dr. Dixon said that this was a case of severe renal disease. They had tried probenecid, and both the serum uric acid and the blood urea fell, but not to normal levels. One sister who had pre-eclamptic toxaemia had been given probenecid, but the effect on renal function in her case could not be assessed.

Prof. S. J. Hartfall (*Leeds*) asked if the progressing chronic nephritis in this case was not linked with the aetiology. With the high level of blood urea one might expect a rise in serum uric acid.

Dr. Dixon replied that, in his experience, the chronically failing kidney was not associated with high serum urate levels. In acute renal disease, in eclampsia, and in the conditions dealt with by the artificial kidney, high levels of serum uric acid were seen, but in chronic nephritis the serum urate seldom rose above 6 to 7 mg. per cent.

In reply to another question, he stated that the parents of the index case were not related.

Dr. A. Aronoff (*Montreal*) said that he had seen two cases of gout precipitated by the use of anti-hypertensive drugs. The first, a patient aged 53, had been given several g. nicotinic acid daily plus chlorothiazide, and had developed an acute attack of gout in the ankle with a rise in serum uric acid to 15 mg. per cent. The second patient, a woman aged 58 with carcinoma of the cervix and essential hypertension, had been started on reserpine and was later given chlorothiazide. This had a marked effect on the hypertension, but the serum uric acid rose from 5·5 to 9·3 mg. per cent. and she developed an acute attack of gout in the right hand.

Dr. Dixon replied that these appeared to be some of the first reported cases of gout caused by treatment with anti-hypertensive drugs. In his experience, chlorothiazide, mecamylamine, pempidine and reserpine had all caused hyperuricaemia, the least effect being from the last. A common pharmacological action seemed likely.

In answer to Dr. Dudley Hart, he stated that the anti-hypertensive drugs did not increase the blood urea.

Prof. E. G. L. Bywaters said that it would be interesting to know more about Dr. Aronoff's patients. He believed that the miscible pool of uric acid had to increase enormously above normal before clinical gout occurred. He wondered whether patients with hypertension had been accumulating uric acid over the years, or whether they had developed gout by a different mechanism, without much deposition of uric acid in the body.

Dr. F. Françon (*Aix-les-Bains*): **Osteo-Articular Reactions after Prostatectomy**. This operation was safer than it used to be, and thus more frequently performed; post-operative complications were thus more often seen, either in the form of infective conditions, including osteitis which varied in severity from mild inflammation to frank suppuration, or in the form of gout.

Among the infective complications, osteitis pubis was the most common. It appeared 1 or 2 months after surgery, especially if the Terence Millin suprapubic approach had been used, and if the patient had had an infected urine. There was pubic and ischial pain, and slight fever (to 100° F.). Radiographic changes usually (but not always) followed, and appeared as bone condensation, or more rarely as rarefaction and erosion. Synostosis was exceptional. The lesion took from 4 to 6 months to heal, less if a retropubic abscess could be found and evacuated, more if the infection were complicated. Nelson (1957) had managed to avoid osteitis

pubis in 410 prostatectomies by taking special precautions to prevent infected retropubic haematomata. In rare cases the intravertebral disks (about 3 months post-operatively), the hips (about 5 months post-operatively), and the tarsus could be involved by the same process. An example of the latter occurring 10 days after prostatectomy was cited. *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* were the organisms most frequently implicated.

Gout had also been seen following prostatectomy. An example was cited of a man aged 70 (with a previous history of chronic tophaceous gout) who had had a most severe attack of acute gouty arthritis in the knee 13 days after operation, which signally failed to respond to colchicine.

The following papers were read by members of the British Association of Physical Medicine and guest speakers:

DR. P. HUME KENDALL and DR. M. E. FEARNLEY (*London*): **Punch Biopsy of the Vertebral Bodies.**

DR. R. GREENWOOD (*Glossop*): **Circulating Antibody Production in Rheumatoid Arthritis.**

DR. R. HARRIS (*Buxton*): **Rehabilitation Results in Rheumatoid Arthritis.**

DR. P. BAUWENS (*London*): **Electrodiagnostic Definition of the Site and Nature of Peripheral Nerve Lesions.**

DR. E. N. COOMES (*Bromley, Kent*): **Correlated Study of Intensity Duration Curves and Terminal Neuronal Re-innervation of Muscles.**

DR. C. M. GODFREY (*Canada*): **Immobilizing Efficiency of Cervical Braces.**

MR. J. C. F. CREGAN (*Manchester*): **Simple Correction of Equinus Deformity in Still's Disease by open Tarsal Crushing.**

BOOK REVIEW

Manifestaciones osteoarticulares de la Brucelosis. By J. Rotes Querol. 1959. Pp. 210, 60 figs, bibl. Editorial JIMS, Barcelona.

This volume, which comes from the University of Barcelona, will bring back memories to those who served in the Mediterranean campaigns of the last war. Brucellosis is still endemic in Spain, and the author was able to collect 174 cases between 1927 and 1955. The ten chapters, each with an English summary, cover all the likely osteo-articular complications of the disease, and illustrate how it may mimic a variety of rheumatic affections. The diagnosis was confirmed by blood culture in 58 per cent. of cases, but serum agglutination was positive in 98 per cent. and complement fixation in 94 per cent. The erythrocyte sedimentation rate is frequently normal.

To the British reader it will appeal as a work of reference. DAVID PREISKEL

SOCIETÀ ITALIANA DI REUMATOLOGIA

Acqui Prizes, 1959

The result of the Fourth Acqui International Prize Competition, for which 28 entries of great scientific merit were received, was announced on September 20, 1959.

The Prizes were presented by Senator Piola, the Financial Under-Secretary, at the end of a scientific session at which papers were given by the foreign members of the panel of judges, Dr. J. Forestier and Prof. P. P. Ravault.

The other members of the adjudicating committee were:

Prof. L. Antognetti, Director of the Medical Clinic of the University of Geneva;
Prof. G. C. Dogliotti, Director of the Medical Clinic of the University of Turin;
Prof. F. Quaglia, Representative of the Medicinal Springs of Acqui-Terme;
Prof. A. Robecchi, Vice-President of the European League against Rheumatism;
Prof. L. Villa, President of the Italian Society against Rheumatism and Director of the Medical Clinic of Milan.

The prize of 1,200,000 lire for original and unpublished work was divided as follows:

G. Sala, G. Ratti, and E. Cirla (*Medical Clinic, Milan*): Researches on the Metabolism of Uric Acid in Normal and Gouty Subjects (500,000 lire).

R. Garelli (*Rheumatism Centre, Turin*): Histological Study of the Structural Changes of the Joint Capsule occurring during Adolescence and Old Age (300,000 lire).

A. Marmont (*Medical Clinic, Gênes*): Critical Review of the Neurovegetative Theory of the Pathogenesis of Scleroderma. Analysis of the Significance of the New Serum Protein Factors (Rheumatoid Factor, L.E. Factor, etc.). (300,000 lire).

H. Fallet, H. Vasey, E. Meyer, and J. Sphar (*Medical Polyclinic, Geneva*): L.E. Cells in Rheumatoid Arthritis (100,000 lire).

The prize of 500,000 lire for a monograph published during the year 1958 was awarded to the book entitled *The Shoulder in Rheumatological Practice*, by S. de Sèze, A. Ryckewaert, and M. Maître (*Hôpital Lariboisière, Paris*).

Ann. rheum Dis. (1959) **18**, 265.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi *of steroid therapy.*

Acute Rheumatism

Rheumatism and Nephritis. (Rheumatismus und Nierenentzündung.) VORLANDER, K. O., FRITZ, K. W., and BRAUN, H. J. (1959). *Münch. med. Wschr.*, **101**, 150. 2 figs, bibl.

In this discussion of the incidence of renal involvement in patients with rheumatoid arthritis or rheumatic fever and its complications, the authors present from the University Medical Clinic, Bonn, their own findings and describe some illustrative cases. Out of a total of 78 patients with rheumatic carditis there were eight cases of renal disease, whereas out of 316 with rheumatoid arthritis only eleven showed such a complication. In the former group all stages of glomerulonephritis as well as focal nephritis were seen, whereas in the latter the usual renal lesion was amyloidosis, nephritis being rare. Some facts and theories regarding the part played by streptococcal infection in the pathogenesis of rheumatic fever and glomerulonephritis are presented and also the possible role of auto-antibodies is briefly discussed.

[Although the authors concede the point earlier made by Hartman and Bland (*Amer. J. Med.*, 1951, **10**, 47; *Abstr. Wld Med.*, 1951, **10**, 105) and by other workers that the coincidental occurrence of rheumatic fever and glomerulonephritis is a rare event, they make no attempt to explore the possible theoretical significance of this point in their discussion of aetiology.]

G. Loewi.

Controlled Study of *beta*-Hemolytic Streptococcal Infection in Rheumatic Families. I. Streptococcal Disease among Healthy Siblings. MILLER, J. M., STANCER, S. L., and MASSELL, B. F. (1958). *Amer. J. Med.*, **25**, 825. 1 fig., bibl.

The incidence of Group-A β-haemolytic streptococcal infections in the siblings of rheumatic children was studied at the House of the Good Samaritan, Boston. From September, 1953, to June, 1956, the subjects were seen regularly at 4-week intervals (except during August and September), when a clinical examination was carried out, throat swabs were taken, and blood for determination of the erythrocyte sedimentation rate (E.S.R.) and the antistreptolysin-O titre was withdrawn. After the first 6 months arrangements were made for home visits should acute febrile respiratory attacks occur. When streptococcal infections developed treatment was instituted with buffered potassium penicillin by mouth or benzathene benzylpenicillin by intramuscular injection. The dosage of the former was at first 200,000 units twice a day for 10 days, but it became clear that while this was suppressive it did not eradicate the streptococci; the dose was therefore increased to 400,000 units 3 times a day. Benzathene benzylpenicillin was given in one injection of 600,000 units. Throat swabs were cultured at about 8 to 10, 12 to 14, and 18 to 20 days after the start of treatment. In all, 235 healthy children were observed for a period of 11,839 "person-weeks". During this period 603 symptomatic respiratory illnesses occurred; 14 per cent. of these were associated with β-haemolytic streptococci, 90 per cent. of the organisms being of Group A. The commonest respiratory illness was coryza which was rarely accompanied by evidence of streptococcal infection. The next most frequent illness was tonsillopharyngitis associated with evidence of Group-A streptococcal infection in 30 per cent. of cases. Half of the cases in which the illness consisted solely of fever were associated with streptococcal infection. Slightly more than 50 per cent. of the infections with Group-A haemolytic streptococci were detected in children who were apparently well. The antistreptolysin-O titre was determined in 76 per cent. of all cases of Group-A haemolytic streptococcal infection, a significant rise in antibody being observed in about 40 per cent. of both symptomatic and asymptomatic cases. This rise occurred in spite of prompt penicillin treatment. Bacteriological relapse occurred in 30 per cent. of patients given the lower dosage of oral penicillin and in 13·8 per cent. of those given the higher dosage. The over-all failure rate in patients receiving benzathene penicillin intramuscularly was 9·1 per cent. No definite case of acute rheumatism occurred, but erythema marginatum was detected in one case and rheumatic heart disease in two, all three cases being in children who had not been treated. In two the streptococcal infection was detected only by the subsequent rise in

antistreptolysin-O titre and one patient had failed to attend the clinic for 2 months after having had a sore throat. The incidence of haemolytic streptococcal disease was higher in children who still had their tonsils than in those without. The peak periods of haemolytic streptococcal disease were late winter and early spring.

C. Bruce Perry.

II. Penicillin Prophylaxis among Rheumatic Fever Subjects, comparing Different Regimes. MILLER, J. M., STANCER, S. L., and MASSELL, B. F. (1958). *Amer. J. Med.*, **25**, 845. Bibl.

A controlled trial of two methods of penicillin administration in the prevention of β-haemolytic streptococcal infections among children convalescing or completely recovered from acute rheumatic fever was carried out at the House of the Good Samaritan, Boston. In-patients received 200,000 units of buffered benzylpenicillin by mouth twice a day, a total of 452 patients being observed for 5,136 "person-weeks". There were no recurrences of rheumatic fever; there was, however, a "breakthrough" of streptococcal infection in two asymptomatic patients, but the carrier state was promptly eradicated by increasing the dose of penicillin to 1·2 million units daily for 10 days. Out-patients were either treated in the same way with oral penicillin (114 patients for 6,545 person-weeks) or were given monthly intramuscular injections of benzathene benzylpenicillin (47 subjects for 2,498 person-weeks). Among the out-patients receiving oral penicillin there were 26 infections (seven symptomatic, nineteen asymptomatic), an infection rate of four per 1,000 person-weeks compared with a rate of 14·5 in untreated siblings. There were two recurrences of rheumatic fever, which were attributed to poor patient co-operation. Among patients given long-acting penicillin intramuscularly there were four infections (one symptomatic and three asymptomatic); three of these occurred on the 28th day after the injection and one on the 34th day in a patient who had failed to report at the usual 4-week interval. The incidence of streptococcal infection in this group was 1·6 per 1,000 person-weeks compared with 13·9 in the siblings. In three of the 452 in-patients a pruritic rash developed, but there were no adverse effects in the out-patients receiving oral penicillin. Reactions to intramuscular injection of benzathene penicillin included varying degrees of pain at the site of the injection (this did not occur with every injection in the same child), occasional local induration with sterile abscess formation, occasional low-grade fever for a day or so following the injection, and hypersensitivity (in two cases).

C. Bruce Perry.

Lesions of Rheumatic Fever in Patients treated with Cortisone. II. The more frequently Involved Viscera. (Las lesiones de la fiebre reumática en los enfermos tratados con cortisona. II. Participación visceral mas frecuente.) COSTERO, I., BARROSO-MOGUEL, R., CHÉVEZ, A., MONROY, G., and CONTRERAS, R. (1958). *Arch. Inst. Cardiol. Méx.*, **28**, 294. 19 figs.

This paper from the National Institute of Cardiology, Mexico City, is a continuation of the authors' previous report on the *post-mortem* findings in a series of thirty patients who died of rheumatic fever while under treatment with cortisone.

Severe fibrinous pericarditis was present in thirteen cases (43 per cent.), the incidence thus being about the same as in patients not treated with cortisone. There was an intense fibroblastic reaction in the pericardium with delayed healing and extensive fibrinoid necrosis. The degree of infiltration of the myocardium and epicardium with lymphoid cells was unaffected by cortisone therapy. Rheumatic pneumonitis was present in eleven cases (37 per cent.) compared with a frequency of 11 per cent. in untreated cases. The characteristic findings were of a slowly organizing exudate, necrosis of the alveolar walls, and interstitial and alveolar haemorrhages, resulting in the formation of many Masson bodies and a diffuse pulmonary fibrosis. There was only one case of rheumatic encephalopathy in this series, the frequency of this complication being very much less than in untreated cases. Rheumatic nephropathy was present in four cases, the lesions consisting in tubular degeneration, dilatation of the afferent arterioles and thickening of the basement membrane of the capillary glomerular loops. In one case a Schiff-positive fibrinoid substance was present in the capillaries and intralobular arterioles.

M. Lubran.

Prophylaxis of Rheumatic Fever. Activity of the Portuguese Institute of Rheumatology in the Medico-Social Field. (A profilaxia da febre reumática. Acção do Instituto Português de Reumatologia neste sector médico-social.) LIMA FALEIRO, A. (1959). *J. Méd. (Pôrto)*, **39**, 285. 18 refs.

Multiple Sclerosis and Rheumatic Fever: Related Diseases. ZIEGLER, D. K. (1959). *Dis. nerv. Syst.*, **20**, 221. 3 figs, 31 refs.

Reserpine in the Treatment of Rheumatic Chorea. (La reserpina nel trattamento della corea reumatica.) SALOMONE, P., and RAINERO, L. (1959). *Aggiorn. pediat.*, **10**, 7. 46 refs.

Rheumatic Fever Prevention. KAIN, T. M. (1959). *J. med. Soc. N.J.*, **56**, 99. 17 refs.

Rheumatic Fever in College Students. GOGGIO, A. F. (1959). *Calif. Med.*, **90**, 151. 4 refs.

Morbid Anatomy of Experimental Streptococcal Infections in Relation to Rheumatic Fever. (Patologická anatomie pokusných streptokokových nákaz ve vztahu k febris rheumatica.) BEDNÁŘ, B. (1959). *Acta Univ. Carol., Med.*, **1**, 1. 28 figs, 16 refs.

Chronic Articular Rheumatism (Rheumatoid Arthritis)

Clinical Significance of the Rheumatoid Serum Factor. KELLGREN, J. H., and BALL, J. (1959). *Brit. med. J.*, **1**, 523. 4 figs, 19 refs.

By correlating the results of estimations carried out

during the years 1952-57 of the agglutinating factor or "rheumatoid factor" in the serum of patients with rheumatoid arthritis and related diseases with the clinical findings the authors have attempted to assess the significance of the agglutinating activity of the serum as a diagnostically specific feature. A single serological technique was employed throughout, this being the standard simple modification of the original sheep-cell agglutination test (S.C.A.T.) of Rose. During the period under review 790 patients were admitted to the rheumatism unit of the Manchester Royal Infirmary. Of the 393 with an initial diagnosis of definite rheumatoid arthritis, 87 per cent. gave a positive S.C.A.T. result on admission, whereas of 41 with probable rheumatoid arthritis, but in whom an alternative diagnosis had been suggested, only 68 per cent. gave a positive result. Among fifteen cases of juvenile rheumatoid arthritis (with onset before the age of 15 years), there were six (40 per cent.) positive results. Positive results were obtained in 51 per cent. of 78 cases of diffuse collagen diseases (systemic lupus erythematosus, systemic sclerosis, and polyarteritis nodosa), but in only 10 per cent. of 229 cases of non-rheumatoid arthritis and in only four out of 34 cases of bone diseases and other miscellaneous diseases.

Of the 393 patients with clinically definite rheumatoid arthritis, subcutaneous nodules were present in 39 per cent., and 100 per cent. of the 62 males and 92 per cent. of the 91 females with nodules gave a positive S.C.A.T. reaction. The proportions were not so high among those who had had the disease for less than one year on admission, even when nodules were present, but in a number of such cases follow-up showed that the original diagnosis of rheumatoid arthritis was incorrect. With the exclusion of these cases, and on the basis of the highest recorded result instead of that of the first test only, a positive S.C.A.T. result was obtained in 96 per cent. of males and 92 per cent. of females with rheumatoid arthritis. In cases of systemic lupus erythematosus and systemic sclerosis a positive reaction to the S.C.A.T. appeared to be related to the presence of articular or peripheral vascular lesions, or both. In eleven cases of confirmed polyarteritis nodosa without rheumatoid arthritis the result was uniformly negative.

Among 1,392 in-patients and out-patients with various polyarthritic syndromes seen during the same period there were 537 cases of ankylosing spondylitis, of which only 4 per cent. gave positive S.C.A.T. results, whereas of 129 cases of atypical spondylitis, 12 per cent. gave positive results. Some of the latter were later diagnosed as cases of rheumatoid arthritis with major spinal involvement, but a high agglutinating titre was not found to be specially associated with peripheral joint involvement as such, since the majority of 62 cases of psoriasis with an inflammatory erosive polyarthritis gave negative results. The proportion of positive results occurring in cases of other types of arthritis was similarly small. Of 190 patients with uveitis attending the Manchester Royal Eye Hospital, only ten gave a positive S.C.A.T. result, six of whom had concomitant clinical evidence of rheumatoid arthritis.

In the course of epidemiological studies a 1-in-10 random sample of all individuals in the age group 55-64 years in the town of Leigh, Lancashire, was studied. Out of 350 subjects tested, nineteen gave a positive S.C.A.T. reaction, of whom eight were shown to have definite and four possible rheumatoid arthritis. Of 94 blood relatives of the nineteen propositi, 20 per cent. gave positive results compared with 5·7 per cent. of a 1-in-30 sample of the adult population (over 25) of the area. It is suggested that the presence of the rheumatoid factor is an index of some inherited metabolic defect predisposing to rheumatoid arthritis and certain other forms of disease that may not yet be fully defined. Conversely, there are a number of forms of erosive polyarthritis not associated with a positive reaction to the S.C.A.T. which need further characterization and investigation, especially in women. *Harry Coke.*

Report of a Three-Year Study on the Systemic and Articular Indexes in Rheumatoid Arthritis. Theoretic and Clinical Considerations. LANSBURY, J. (1958). *Arthr. and Rheum.*, **1**, 505. 9 figs, 10 refs.

[The evaluation of the progress of rheumatoid disease is a problem of vital importance to all rheumatologists, and a number of schemes have been devised to that end. Of these schemes, that devised by the author and his co-workers, is perhaps the one most worthy of detailed consideration, as being the most complete and "scientific", and this paper should be carefully studied by all rheumatologists.]

A report is presented from Temple University School of Medicine, Philadelphia, on a 3-year study of the value of the systemic and articular indices previously described by the author (*Ann. rheum. Dis.*, 1958, **17**, 101). These are designed to provide an objective and accurate method of assessment of the inflammatory manifestations of rheumatoid arthritis and the structural changes which accompany them. They are expressed as numerical values arrived at from assessment of such factors as the degree of stiffness, amount of pain, and muscle weakness, the total joint inflammation, and the erythrocyte sedimentation rate.

The author considers that a strong case can be made for believing that this method of evaluation will present an accurate record of changes in disease activity. He points out that although the systemic and the articular indices are independently based upon different data, they show nevertheless a significant degree of parallelism in their results, and that these accord closely with the general over-all clinical estimate of changes in disease activity. Before these indices can be recommended for general use he suggests that the matter should be further investigated by a committee of independent observers on a multi-clinic basis. *W. S. C. Copeman.*

Regression of Amyloidosis Secondary to Rheumatoid Arthritis. PARKINS, R. A., and BYWATERS, E. G. L. (1959). *Brit. med. J.*, **1**, 536. 3 figs, 26 refs.

Only two cases of apparent recovery from amyloidosis secondary to rheumatoid arthritis have been reported; in neither case was there a long follow-up or histological

proof of the presence of amyloidosis. In this paper from the Postgraduate Medical School of London and the Canadian Red Cross Memorial Hospital, Taplow, Berks., the clinical progress of two patients with severe generalized rheumatoid arthritis complicated by amyloidosis is described. The first patient, a girl, had had arthritis from the age of 3 years; amyloid disease was diagnosed when she was 8 years old and during the next 7 years the clinical signs of this disease regressed twice in parallel with remissions of rheumatoid arthritis. When the patient was 15 years old the nephrotic syndrome developed, unassociated with increased joint activity, and there was some retention of urea, indicating that amyloid deposits had not been absorbed in the periods of clinical improvement. The second patient, a man, developed rheumatoid arthritis at the age of 28 and amyloid disease was diagnosed a year later. Treatment with high doses of cortisone was followed by a remission in both the rheumatoid activity and the signs of amyloid disease. Three years later both conditions relapsed in spite of maintenance therapy with cortisone in a dosage of 50 mg. daily; the dosage of cortisone was then increased to 200 mg. daily, with improvement in both joint activity and signs of amyloid disease, the improvement being maintained with a dosage of 125 mg. daily. Biopsy examination of the liver and kidney, however, showed that amyloid had not been reabsorbed.

The authors briefly discuss two further patients, both females, with amyloidosis secondary to rheumatoid arthritis who were treated with prednisolone. In both patients the dosage needed to suppress the joint symptoms caused peptic ulceration and the drug had to be withdrawn; no significant changes in the clinical or biochemical state were noted. Triiodothyronine was also given to two patients without apparent improvement in the amyloidosis.

The authors conclude that "there does not seem to be any histologically proved case of recovery from amyloidosis secondary to rheumatoid arthritis". The disappearance of clinical signs does not mean reabsorption of amyloid. Steroid hormones do not appear to influence the disease unfavourably and may have induced remission in two of their cases. *K. C. Robinson.*

Activity of Rheumatoid Arthritis and Plasma 17-hydroxycorticosteroids during Pregnancy and following Parturition. [In English.] OKA, M. (1958). *Acta rheum. scand.*, **4**, 243. 13 refs.

A comparison between the clinical symptoms and free plasma 17-hydroxycorticosteroids (17-OHCS) levels was made in two patients with rheumatoid arthritis during pregnancy and after delivery. The free plasma 17-OHCS was elevated in both cases but, whereas there was the expected clinical improvement in one patient, there was aggravation of symptoms in the other. The conjugated plasma 17-OHCS was low in both cases suggesting an altered 17-OHCS metabolism. It is thought most probable that the main fraction of reacting material in the plasma of the patient with aggravation of symptoms was not hydrocortisone but biologically inert tetrahydrocortisone. *G. W. Csonka.*

Comparative Evaluation of Newer Corticosteroids in the Treatment of Rheumatoid Arthritis. WILLIAMS, G. T. (1959). *Sth. med. J.* (*Bgham, Ala.*), **52**, 267. 2 figs, 8 refs.

Desametazone, a New Methylated Corticosteroid. Evaluation of Its Clinical and Biological Action in Patients with Rheumatoid Arthritis. (Desametasone, nuovo corticosteroide metilato. Valutazione clinico-biologia in pazienti affetti da artrite reumatoide.) LUCHERINI, T., CECCHI, E., and FERRARIS, F. (1959). *Clin. ter.*, **16**, 3. 8 figs, 7 refs.

Critical Study of Felty's Syndrome. (Étude critique du syndrome de Felty.) LAYANI, F., DURUPT, L., and AMOR, B. (1959). *Sem. Hôp. Paris*, **35**, 1282. 30 refs.

Contact-Type Delayed Hypersensitivity in Patients with Rheumatoid Arthritis. EPSTEIN, W. L., and JESSAR, R. A. (1959). *Arthr. and Rheum.*, **2**, 178. 11 refs.

Senile Rheumatoid Arthritis. (La polyarthrite chronique évolutive sénile.) VIGNON, G., DURANT, J., BOUCHET, F., and NAHAS, V. (1959). *Rev. lyon. Méd.*, **8**, 157. 14 refs.

Clinical, Radiological, and Serological Findings in 41 Cases of Rheumatoid Arthritis originating in Old Age. (Rilievi clinici, radiologici e sierologici in 41 casi di artrite reumatoide insorta in età senile.) EINAUDI, G. (1959). *Reumatismo*, **11**, 31. 15 refs.

Juvenile Rheumatoid Arthritis in New York City. MANHEIMER, R. H., GREENE, K. R. C., and KROLL, F. (1959). *Arch. Pediat.*, **76**, 173. 7 refs.

Differential Diagnosis in Rheumatoid Arthritis. [In English.] SVARTZ, N. (1958). *Arch. interamer. Rheum.*, **1**, 615. 5 figs, 24 refs.

Antimalarials in the Treatment of Rheumatoid Arthritis. CATLETT, J. B., and DINSMORE, H. (1959). *Va med. Monthly*, **86**, 217. 12 refs.

Use of Synthetic Antimalarial Drugs in Rheumatoid Arthritis. (Der Gebrauch synthetischer Antimalariamittel bei der primär chronischen Polyarthritis.) KUIPERS, R. K. W. (1959). *Z. Rheumaforsch.*, **18**, 197. 8 refs.

Iron Treatment of Anaemia in Rheumatoid Arthritis. LÖVGREN, O. (1959). *Acta rheum. scand.*, **5**, 66. 10 refs.

Value and Complications of Gold Therapy in Rheumatoid Arthritis. EDSTRÖM, G. (1959). *Acta rheum. scand.*, **5**, 53. 3 figs, 19 refs.

Studies of the Etiology of Rheumatoid Arthritis. III. Experimental Production of Arthritis in Rabbits following Focal Infection of Paranasal Sinus with Haemolytic Streptococcus. SHIMIZU, G., SHICHIKAWA, K., and TAKIUCHI, K. (1958). *Med. J. Osaka Univ.*, **9**, 447. 12 refs.

Rheumatoid Arthritis—A Collagen Disease. SADRE ALAM, A. (1959). *Medicus* (*Karachi*), **18**, 71. 3 refs.

On the Metabolism of Amino Acids and Proteins in Rheumatoid Arthritis. NETTELBLADT, E. (1959). *Acta rheum. scand.*, **5**, 49. 5 refs.

Peripheral Neuritis in Rheumatoid Arthritis. (Les névrites périphériques de la polyarthrite chronique évolutive.) VIGNON, G., and DURANT, J. (1959). *Rev. lyon. Méd.*, **8**, 137. 35 refs.

Synovial Fluid in Rheumatoid Arthritis. (O líquido sinovial na artrite reumatóide.) HOULI, J., and PINHEIRO, J. (1959). *Arch. interamer. Rheum.*, **2**, 46. 43 refs.

Electromyographical and Electrical Investigations in Rheumatoid Arthritis. (Badania elektromiograficzne i elektryczne w gośćcu pierwotnie przewleklym.) MAJKOWSKI, J. (1959). *Pol. Tyg. lek.*, **14**, 801. 1 fig., 7 refs.

Respiratory Function in Rheumatoid Arthritis. (Il quadro respiratorio nell'artrite reumatoide.) GHIRINGHELLI, G., TANSINI, G., and RIMOLDI, R. (1959). *Osped. maggiore*, **47**, 230. 5 figs, 32 refs.

Psychological Evaluation of the Effect of a Psychotrophic Drug ["Pipradrol"] on Patients with Rheumatoid Arthritis [Preliminary Communication]. (Valutazione psicologica dell'azione esercitata da un farmaco psicotropo negli ammalati di artrite reumatoide.) MADERNA, A. M., and PIMPINELLI, E. (1959). *Reumatismo*, **11**, 41. 18 refs.

Synergistic Action of Isoniazide and Prednisone in the Treatment of Rheumatoid Arthritis. (Kombinerad Effekt av Isoniazid och Prednison vid Ledgangsreumatism.) KIRPILA, J., and RIPATTI, N. (1959). *Nord. Med.*, **61**, 782. 1 fig., 6 refs.

Rheumatoid Heart Disease. MISRA, S. S., PRAKASH, S., TEOTIA, S. P. S., and AGRAWAL, P. L. (1959). *J. Indian med. Ass.*, **32**, 362. 13 refs.

Medical Rehabilitation of Rheumatoid Arthritis. PAUL, W. D. (1959). *J. Iowa St. med. Soc.*, **49**, 203. 7 refs.

(Osteo-Arthritis)

Intra-Articular Alkali Therapy in Osteo-Arthritis of the Hip and Knee. (Die intra-artikuläre Alkalitherapie der Arthrosis deformans de Hüft- und Kniegelenke.) KEUSENHOFF, W. (1959). *Z. ärztl. Fortbild.*, **53**, 412.

Treatment of Osteo-Arthritis of the Knee with Intra-Articular Injection of Crystalline Suspension of "Decortin-H" (Prednisolone) and Prolonged Bandaging with "Ichtholan". (Behandlung der Kniegelenksarthrosen mit intraartikulärer Decortin-H-Kristallsuspension und Ichtholan-Dauerverband.) EONHARDT, H. (1959). *Münch. med. Wschr.*, **101**, 974.

Organic Protein Lysates in the Treatment of Chronic Degenerative Joint Disease. (La terapia a base di lisati proteici di organo nel trattamento delle artropatie croniche a tipo degenerativo.) BERGAMI, P. (1959). *Minerva med.* (*Torino*), **50**, 1592. 12 refs.

Balneotherapy in Osteo-Arthritis. (Balneotherapie der Arthrosen.) SCHOGER, G. A. (1959). *Z. Rheumaforsch.*, **18**, 182. 3 figs.

Value of Phenylbutazone (Butazolidin) in Generalized Osteo-Arthritis. RAMOS, J. M. (1959). *R.I. med. J.*, **42**, 249.

Ligament Relaxation and Osteo-Arthritis. Loose Jointed *v.* Close Jointed. HACKETT, G. S. (1959). *Rheumatism*, **15**, 28. 3 figs, 11 refs.

Painful Post-Menopausal Vertebral Tropho-Postural Syndrome. DE SÈZE, S. (1959). *Rheumatism*, **15**, 24.

Degenerative Joint Disease at the Climacteric. (Die degenerativen Gelenkerkrankungen im Klimakterium.) SCHULER, B. (1959). *Z. Rheumaforsch.*, **18**, 1. 115 refs.

(Spondylitis)

Amyloidosis in Chronic Polyarthritis. (Amyloidose og Polyarthritis Chronica.) ASLAKSEN, B. B. (1959). *T. norske Laegeforen.*, **79**, 49. 2 figs, 25 refs.

In this paper from the Stokmark District Hospital, Norway, the author reports two cases of ankylosing spondylitis which he considered to be in two stages of amyloidosis.

The first patient, a 41-year-old man, had shown signs of progressive lumbo-sacral spondylosis over a period of 17 years, and had also developed effusions into first one and then both knee joints. Over the last few years there had been intermittent albuminuria, and sternal puncture revealed the presence of plasma cells. Serum electrophoresis revealed a lowered serum albumin (1·7 g./100 ml.) and raised α^2 and γ globulin levels. Skin and lymph gland biopsies were normal.

The second patient, a 46-year-old man, had developed ilio-sacral ankylosis, associated with effusions into both knee joints, oedema, and marked albuminuria. Electrophoresis again revealed a lowered serum albumin (0·5 g./100 ml.), a markedly raised α^2 globulin (2·1 g./100 ml.), with the γ globulin at the upper limit of normal (1·6 g./100 ml.). Skin biopsy confirmed the presence of amyloid deposits, and a lowered 17-ketosteroid excretion (1·2 mg./24 hrs) suggested early infiltration of the adrenals.

These cases are discussed in the light of Teilum's two-phase theory, the first being accordingly in the active pyroninophilic phase corresponding to Selye's stage of resistance, whereas the second had reached the negative amyloid, phase corresponding to Selye's stage of exhaustion. *H. F. Reichenfeld.*

Physical Findings in Early Rheumatoid Spondylitis. WALLACE, S. L. (1959). *N.Y. St. J. Med.*, **59**, 2379. 10 refs.

Treatment of Ankylosing Spondylitis by Physical Methods. (Le traitement de la spondylarthrite ankylosante par les moyens physiques.) LAYANI, F., LEHMANN, C., and PEYRON, J. (1959). *Ann. Med. phys.*, **2**, 15.

Treatment of Ankylosing Spondylitis. (Zur Therapie der Spondylarthritis ankylopoietica.) KUIPERS, R. K. W. (1959). *Z. Rheumaforsch.*, **18**, 31. 5 refs.

Long-Term Treatment of Active Ankylosing Spondylitis with Small Doses of Adrenocortical Hormones. (Langzeitbehandlung des aktiven Morbus Bechterew mit kleinen Dosen von Nebennierenrinden-Hormonen.) TREIBER, W. (1959). *Z. Rheumaforsch.*, **18**, 36. 5 figs, 14 refs.

Agglutination Reaction with Sensitized Sheep Erythrocytes in Ankylosing Spondylitis. (Die Agglutinationsreaktion mit sensibilisierten Hammelblutkörperchen bei Morbus Bechterew.) WÖLLNER, D., and FUCHS, W. (1959). *Dtsch. Arch. klin. Med.*, **205**, 463. 27 refs.

Clinical Position of Ankylosing Spondylitis. (Zur klinischen Stellung der Spondylitis ankylopoietica [Morbus Strümpell-Marie-Bechterew].) OTT, V. R. (1959). *Z. Rheumaforsch.*, **18**, 14. 3 figs, 66 refs.

Aortitis and Aortic Regurgitation associated with Rheumatoid Spondylitis. TOONE, E. C., JR., PIERCE, E. L., and HENNIGAR, G. R. (1959). *Amer. J. Med.*, **26**, 255. 12 figs, 19 refs.

Atypical Clinical and Radiological Course of Ankylosing Spondylitis. (Der atypische Verlauf der Spondylarthritis ankylopoietica in Klinik und Rontgenbild.) OTTO, W. (1959). *Z. Rheumaforsch.*, **18**, 27. 4 figs, 12 refs.

(Miscellaneous)

Effect of Corticosteroids on the Skin Response to Ultra-Violet Light in Rheumatoid Arthritis. BANERJEE, S. K., and HARRIS, R. (1958). *Ann. phys. Med.*, **4**, 288.

The skin response to ultra-violet light and the effect of corticosteroid therapy in active rheumatoid arthritis were studied in ten patients at the Devonshire Royal Hospital, Buxton. Graded exposures were used in each test, the test being repeated twice before corticosteroid therapy was started and at intervals thereafter. The dosage of corticosteroids employed (up to 30 mg. per day of prednisolone or its equivalent) was sufficient to depress the erythrocyte sedimentation rate and increase the haemoglobin level. A variation in skin response was noted, but there was no consistent trend, and the authors conclude that corticosteroid therapy does not modify the skin reaction to ultra-violet light in patients with rheumatoid arthritis. *A. St. J. Dixon.*

Osmic Acid in Arthritis Therapy. BERGLÖF, F. E. (1959). *Acta rheum. scand.*, **5**, 70. 3 figs, 1 ref.

Treatment of Arthritis with a Dextro-Amphetamine-Analgesic Combination. STRAZZA, J. A., JR. (1959). *J. med. Soc. N.J.*, **56**, 124.

Effect of Intra-Articular Hydrocortisone Therapy upon the Joint Temperature in Osteo-Arthritis and Rheumatoid Arthritis. WRAMNER, T. (1959). *Acta rheum. scand.*, **5**, 59. 3 figs, 21 refs.

Treatment of Tennis Elbow with Special Reference to the Injection of Corticosteroids. (L'epicondilalgia e i suoi trattamenti locali, con particolare riguardo alle iniezioni di steroidi della serie cortisonica.) GARELLI, R. (1959). *Reumatismo*, **11**, 71. 33 refs.

Treatment of Scapulo-Humeral Periarthritis with Alpha-Chymotrypsin. (Nouveaux apports au traitement de la périarthrite scapulo-humérale avec l'alpha-chymotrypsine.) BANOS, J. G., and DEL VALLADO, P. F. (1958). *Rhumatologie*, **10**, 275. 34 refs.

Epidemic Polyarthritis. ANDERSON, S. G. (1959). *Rheumatism*, **15**, 34. 1 fig., 15 refs.

Bacterial Arthritis: Experiences in the Treatment of 77 Patients. CHARTIER, Y., MARTIN, W. J., and KELLY, P. J. (1959). *Ann. intern. Med.*, **50**, 1462. 11 refs.

Disk Syndrome

Late Prognosis in Lumbar Disk Herniation. SPARUP, K. H. (1959). *Acta rheum. scand.*, **5**, 75.

Disabilities due to Degenerative Changes in the Lumbar Intervertebral Disks and Their Treatment. (Beschwerden bei degenerativen Veränderungen an der Lendenwirbelsäule und ihre Therapie.) SCHOGER, G. A., and ERNESTI, H. J. (1959). *Z. Rheumaforsch.*, **18**, 113. 8 refs.

Degenerative Arthritis of the Lumbo-Sacral Joint. WILSON, J. C., JR. (1959). *J. Amer. med. Ass.*, **169**, 1437. 7 figs, 10 refs.

Neurological and Radiological Manifestations associated with Spondylosis of the Cervical and Lumbar Spine. EPSTEIN, J. A., and EPSTEIN, B. S. (1959). *Bull. N.Y. med. Coll.*, **35**, 370. 3 figs, 14 refs.

Osteo-Arthritis of the Cervical Spine. COHEN, A., SEVEN, M. J., KANENSON, W. L., and GOLDMAN, J. (1959). *Penn. med. J.*, **62**, 548. 2 refs.

Gout

Gout and Diabetes. HERMAN, J. B. (1958). *Metabolism*, 7, 703. 2 figs, 9 refs.

It was shown by Bornstein and Lawrence (*Brit. med. J.*, 1951, **2**, 1541; *Abstr. Wld Med.*, 1952, **11**, 256) that lack of insulin need not be the only cause of diabetes. Experimentally diabetes can be produced by the administration of alloxan, a metabolite of uric acid. The author therefore suggests that some cases of diabetes may result from an abnormality in the breakdown of nucleoprotein. If this hypothesis is correct a decrease in carbohydrate tolerance should occur in patients with gout.

At the Harvard School of Public Health, Boston, 82 gouty patients were therefore investigated, 27 non-gouty arthritic patients serving as a control group. There was a distinctly higher proportion of patients with a reduced glucose tolerance among those suffering from gout than in the control group. From this the author concludes that there exists some factor specifically related to gout which is responsible for the observed abnormality in carbohydrate metabolism. *R. Schneider.*

Probenecid (Benemid) in the Treatment of Gout and Gouty Arthritis. RICE, F. A. (1959). *Minn. Med.*, **42**, 209. 2 figs, 19 refs.

Preliminary Experience of the (Uricosuric) Action of G.28315. (Primeras experiencias sobre la accion del G 28315.) RUIZ MORENO, A. (1959). *Arch. argent. Reum.*, **22**, 11.

Precipitating Factors in Attacks of Gout. (Los factores precipitantes del ataque de gota.) RUIZ MORENO, A. (1959). *Arch. argent. Reum.*, **22**, 16.

Testicular Factors and Uric Acid. (Facteurs testiculaires [testosterone, hyaluronidase] et acide urique.) MACALUSO, M. P. (1959). *Rev. Rhum.*, **26**, 106. 13 refs.

Pararheumatic (Collagen) Diseases

Frequency, Prognosis, and Early Diagnosis of Periarteritis Nodosa. LJUBOMUDROV, V. E. (1959). *Ter. Arh.*, **31**, 50. 15 refs.

Periarteritis nodosa has been recognized as a disease entity for 90 years, but it is still imperfectly known and, in its formes frustes, is very often missed. Consequently its mortality has probably been much exaggerated. An analysis of the records of 1,019 cases from 1866 to 1957 showed that the diagnosis was made during life in only 36 per cent. of cases over the whole period, and even in the last 12 years it was established before death in only 42·6 per cent. Of the 368 patients in whom the disease was diagnosed during life, 180 (48·9 per cent.) were discharged home substantially improved. Of those diagnosed on clinical grounds, 76·4 per cent. died, while among those in whom the diagnosis was made by biopsy the death rate was only 27 per cent., those cases in which diagnosis was based on the histological findings in organs removed at operation occupying an intermediate position with 50 per cent. mortality.

It is therefore possible that with the more frequent recognition of mild forms of the disease the mortality would prove to be still lower, since many of these cases evidently undergo spontaneous recovery. Early recourse to biopsy in cases of a general disorder with symptoms implicating a number of organs or systems would probably reveal the incidence of the disease to be higher and its mortality lower than is generally believed at present.

L. Firman-Edwards.

Sjögren's Syndrome and Systemic Lupus Erythematosus. HEATON, J. M. (1959). *Brit. med. J.*, **1**, 466. 38 refs.

The clinical and pathological features in 28 consecutive cases of Sjögren's syndrome, seen at the Bristol Eye Hospital over a period of 9 months, are described. The patients, all females, were aged from 35 to 83 years, the majority being over 50. Ocular symptoms, which had been present for 1 to 18 years, consisted in cessation or diminution of secretions from the lacrimal glands. Similar changes were observed in the salivary glands and the submucous glands of the respiratory and upper alimentary tracts. The lacrimal glands showed connective tissue proliferation and fibrosis, with atrophy of the glandular tissue. In the conjunctiva oedema of the epithelial and sub-epithelial layers, with marked thinning of the epithelium in the later stages, and destruction of the elastic tissue were observed. The changes in the cornea were similar. In addition to these classic lesions seventeen patients had rheumatoid arthritis and a further nine had arthralgia. Other associated conditions were chilblains and/or Raynaud's phenomenon in twelve cases and leucopenia and thrombocytopenia respectively in sixteen and fourteen out of 24 cases. Electrophoresis of the serum proteins revealed a lowered albumin level in fifteen patients and raised α^2- and γ-globulin levels in sixteen and seventeen patients respectively. In all cases peripheral blood was examined for the presence of L.E. cells on three occasions at intervals of about 3 weeks, these being found in ten cases. Mikulicz's disease was present in two cases in the series, in both of which L.E. cells were found. Of two cases of Felty's syndrome (leucopenia, splenomegaly, and rheumatoid arthritis) one gave a positive reaction to the L.E.-cell test.

In a comparison of the clinical and pathological features of Sjögren's syndrome with those of systemic lupus erythematosus, the author finds a number of similarities. He states that L.E. cells are not always found in known cases of systemic lupus erythematosus, nor have they been looked for systematically in cases of Sjögren's syndrome. He suggests that prolonged

follow-up of these cases would give further evidence in favour of his hypothesis. *H. F. Reichenfeld.*

Intravenous Procaine in the Management of Some Cutaneous Manifestations of Collagen Diseases. FARRINGTON, J. (1958). *Sth. med. J.* (*Bgham, Ala.*), **51**, 1426. 6 figs, 7 refs.

Procaine has been described as having an anti-histaminic effect, an anti-acetylcholine (nerve blocking) effect, a direct action on cells (especially nerves and endothelial cells), and an adrenaline-potentiating effect. The results obtained with intravenous administration of procaine in balanitis xerotica obliterans and lichen sclerosus et atrophicus were encouraging, and suggested a trial of this drug in morphoea, acrosclerosis, generalized (systemic) scleroderma, and dermatomyositis, 71 cases of scleroderma of all types and four of dermatomyositis being so treated. All the patients were admitted to hospital and given 0·1 g. Seconal (quinalbarbitone) by mouth 20 minutes before treatment with procaine started. Initially 500 ml. 0·1 per cent. procaine in normal saline or in 5 per cent. glucose solution was given; if no untoward reaction was observed 1,000 ml. was given once a day for the succeeding 6 days at a rate of 45 drops a minute. This course was repeated at intervals of 6 weeks, but if there was no improvement after the third course, treatment was stopped. None of the patients received more than twelve courses or fewer than three.

From the results the author concluded that intravenous infusion of procaine tended to delay progression of certain cutaneous manifestations of some collagen diseases, especially acrosclerosis with Raynaud's phenomena and peripheral ulceration. *E. W. Prosser Thomas.*

Pulmonary Manifestations in Collagen Diseases. NICE, C. M., MENON, A. N. K., and RIGLER, L. G. (1959). *Amer. J. Roentgenol.*, **81**, 264. 12 figs, 39 refs.

The authors have reviewed the case records and radiographs of 109 patients admitted to the University of Minnesota Hospitals during the 15 years 1942-56 with collagen diseases. There were forty cases of periarteritis nodosa, 37 of disseminated lupus erythematosus, twenty of scleroderma, seven of dermatomyositis, and five of rheumatic pneumonitis. In 75 cases the diagnosis was confirmed by means of necropsy or biopsy. Radiological abnormalities in the lungs, pleura, or heart were demonstrated in about two-thirds of the cases, and details of twelve of these are given to illustrate the principal abnormalities found and those combinations of *x*-ray features which may be of diagnostic significance.

The association of "interstitial pneumonitis" and pleural effusion is stated to be suggestive of collagenosis, and the addition of non-specific cardiac enlargement and prominent hilar shadows in the absence of peripheral pulmonary congestion makes the diagnosis even more likely. The presence of interstitial fibrosis and emphysema is similarly suggestive when confined to the lower and the middle zones and accompanied by small, cyst-like changes, while the combination of these with non-specific cardiac enlargement, lack of peristalsis and widening of the oesophagus, and subcutaneous calcification is diagnostic of scleroderma. Pleural and pericardial effusions occurring together favour the diagnosis of disseminated lupus erythematosus or rheumatic pneumonitis, and hilar vascular prominence is a frequent finding in periarteritis nodosa. *D. E. Fletcher.*

Analysis of the Precipitation Test for Systemic Lupus Erythematosus. PEARSON, C. M. (1959). *J. Amer. med. Ass.*, **169**, 30. 7 refs.

The specificity of the recently described *p*-toluenesulphonic acid test for systemic lupus erythematosus (*J. Amer. med. Ass.*, 1958, **166**, 1424; *Abstr. Wld Med.*, 1958, **24**, 214) was studied in 25 patients with this disease at the Wadsworth Hospital, Veterans Administration Center, Los Angeles. A positive reaction to the test was obtained with serum from six of the patients, but the results did not appear to correlate with disease activity. Of 100 tests carried out on serum from 94 patients with rheumatoid arthritis, 32 gave positive results, as did a large proportion of tests on sera from patients with other collagen diseases. A positive reaction was also obtained with serum from seven of 58 patients with non-rheumatic diseases.

It is concluded that the test is not specific for systemic lupus erythematosus. [This is in accord with the published work of others.] *M. Wilkinson.*

Precipitin Reaction between DNA and a Serum Factor in Systemic Lupus Erythematosus. DEICHER, H. R. G., HOLMAN, H. R., and KUNKEL, H. G. (1959). *J. exp. Med.*, **109**, 97. 7 figs, 44 refs.

Interaction between a nuclear material, possibly deoxyribonucleic acid (DNA), and the serum of patients suffering from systemic lupus erythematosus (S.L.E.) has now been demonstrated by a variety of techniques. The present study from the Rockefeller Institute, New York, reports its demonstration as a precipitin reaction by means of a double diffusion technique in agar. The reaction was positive in eight out of fourteen cases of active S.L.E., whereas negative results were obtained with serum from six healthy subjects and an unstated number of control subjects with other diseases. Preparations of DNA from different animal and even bacteriophage sources were precipitated equally well.

Quantitative precipitin curves obtained with three of the positive sera were characteristic of an antigen-antibody union, with zones of antibody excess, equivalence, and antigen excess. Complement was observed to be fixed in the reaction. Partial dissociation of the precipitate by deoxyribonuclease yielded a γ globulin which reacted with DNA and with whole nuclei, but did not induce L.E.-cell formation. On the other hand the sera continued to induce L.E.-cell formation even after removal of the DNA precipitate.

The authors consider that the DNA-precipitating factor found in the serum of some patients with S.L.E. is distinct from the L.E.-cell factor and is one of a number of autoantibodies elicited in this disease.

M. Wilkinson.

Periarteritis Nodosa and Pigmentary Retinitis. (Periartérite noueuse et rétinite pigmentaire.) DÉJEAN, C., and CHAMPION, J. (1958). *Montpellier méd.*, **53**, 697. 12 refs.

A case of periarteritis nodosa with pigmentary retinitis is reported; the pathogenesis of the retinal changes is discussed, they are probably due to retinal arterial sclerosis instigated by periarteritis. *S. Vallon.*

Involvement of the Eyes in Periarteritis Nodosa. BLODI, F. C., and SULLIVAN, P. B. (1959). *Trans. Amer. Acad. Ophthal. Otolaryng.*, **63**, 161. 6 figs.

Case report of periarteritis nodosa in which a hypertensive retinopathy with globular retinal detachment was found to be associated histologically with scattered foci of non-granulomatous uveitis (without obvious involvement of the choroidal vessels), while an active periarteritis, amply evident systemically, was found only around the episcleral and orbital vessels.

P. D. Trevor-Roper.

Cardiovascular Changes in Systemic Lupus Erythematosus. (Las alteraciones cardiovasculares en el lupus eritematoso sistémico.) PURRIEL, P., BOUTON, J., PERONI, R., YANNICELLI, E., MARTINEZ, J. A., and FERREIRA, W. A. (1958). *Tórax*, **7**, 267. 19 figs, 47 refs.

Clinical Evaluation of a Simple Precipitation Test for Systemic Lupus Erythematosus. [In English.] VARTIO, T. (1959). *Ann. Med. exp. Fenn.*, **37**, 86. 3 refs.

Periarteritis Nodosa and the Nervous System. (Polyarteritis Nodosa og Nervesystemet.) KOPPANG, K. (1959). *T. norske Laegeforen.*, **79**, 679. 23 refs.

Disseminated Lupus Erythematosus. (Lupus Erythematosus Disseminatus.) BICHEL, J., HOLTEN, C., and PETERSEN, V. P. (1959). *Ugeskr. Læg.*, **121**, 933. 30 refs.

Respiratory Manifestations of the Collagen Diseases with Reference to Two New Observations. (Manifestations respiratoires des collagénoses.) JARNIOU, A.-P., BAYLON, H., MOREAU, A., and ENJALBERT, M. (1959). *Sem. Hôp. Paris*, **35**, 2090. 8 figs, 6 refs.

Collagen Diseases and Related Reaction Diseases. (Die Kollagenosen und verwandte Reaktionskrankheiten.) FANCONI, G. (1959). *Münch. med. Wschr.*, **14**, 581. 4 figs, 17 refs.

Experimental Attempt to produce L.E. Syndrome (Arthritis) in Swine with Hydralazine. MCCOY, F. W., and LEACH, W. J. (1959). *Proc. Soc. exp. Biol. (N.Y.)*, **101**, 183. 5 refs.

Dexamethasone in the Treatment of Dermatomyositis. (Il desametazone nella terapie della dermatomiosite.) DE ROSA, F. (1959). *Rif. med.*, **73**, 438. 9 figs, 5 refs.

The Hand in Scleroderma. GORDON, S. (1959). *Plast. reconstr. Surg.*, **23**, 240. 4 figs, 6 refs.

Progressive Scleroderma. (Esclerodermia progressiva.) RIBEIRO SANTOS, V. A., MONTEIRO BAPTISTA, L. M., and GOMES MELEIRO (1958). *Bol. clin. Hosp. Lisboa*, **22**, 415. 28 figs, 27 refs.

Classification of Generalized Scleroderma in the Adult. (Sistematizacion de las esclerodermias generalizadas del adulto.) PIERINI, LUIS E. (1958). *Arch. argent. Derm.*, **8**, 285. 16 refs.

Chloroquine in the Treatment of the "Collagenoses". (La chloroquine dans le traitement des "collagénoses".) LAYANI, F., and RINGENBACH, C. (1959). *Sem. Hôp. Paris*, **35**, 1290. 17 refs.

General Pathology

Partial Purification and Properties of the Lupus Erythematosus Cell Promoting Factor. WILLKENS, R. F., DRESCHLER, M., and LARSON, D. L. (1958). *Proc. Soc. exp. Biol.*, **99**, 645. 2 figs, 12 refs.

Working at the Columbia University College of Physicians and Surgeons and at the Presbyterian Hospital, New York, the authors have achieved considerable purification of the L.E. cell factor. Gamma globulin from serum of patients with systemic lupus erythematosus was first separated electrophoretically and further purification was by column chromatography using a cationic cellulose exchanger and eluting with 0·15M saline at pH 7. The product induced rosettes but not L.E. cells, and gave a strongly positive DNA-protein coated latex agglutination test. It showed a single electrophoretic peak with the mobility of normal gamma globulin and a sedimentation constant of 7 Svedberg units. Agar diffusion studies suggested a single antigenic component behaving identically with a component of normal gamma globulin but not reacting with purified desoxyribo-nucleic acid. The authors suggest that the L.E. cell factor shares antigenic groupings with normally occurring gamma globulin. *M. Wilkinson.*

Pathology of Crico-arytenoid Arthritis. MONTGOMERY, W. W. (1959). *New Engl. J. Med.*, **260**, 66. 6 figs, 7 refs.

This paper gives a short description of this condition, together with notes on two cases. Crico-arytenoid arthritis is most commonly associated with generalized arthritis, usually of the rheumatoid variety. It may, however, be of traumatic origin or it may sometimes be caused by inflammation spreading from neighbouring

structures. Immobilization may result in ankylosis of the joints. In the acute stage, there may be pain, dysphagia, hoarseness, and dyspnoea. Pressure on the thyroid cartilage produces pain. Examination of the larynx shows redness and swelling in the arytenoid region. In the chronic condition, the arytenoids are immobile and there is laryngeal stridor. In two cases of rheumatoid arthritis with laryngeal symptoms seen by the author, histological examination of the crico-arytenoid joints revealed some loss of articular cartilage and fibrosis involving the joint space. [These details are not adequate for the histological diagnosis of rheumatoid arthritis.] *G. Loewi.*

Simple, Rapid Diagnostic Test for Rheumatoid Arthritis—Bentonite Flocculation Test. BLOCH, K. J., and BUNIM, J. J. (1959). *J. Amer. med. Ass.*, **169**, 307. 3 figs, 16 refs.

A rapid diagnostic aid in rheumatoid arthritis, the bentonite flocculation test, which is a modification of a serological test for the detection of *Trichinella* antibodies, is described in this paper from the National Institutes of Health, Bethesda, Maryland. Bentonite is a naturally occurring clay which is suspended in distilled water. The particles are coated with human gamma globulin and methylene blue is added to make them readily visible. The coated bentonite particles are then added to serial saline dilutions of inactivated sera to be tested on slides. The result is considered to be positive when at least 50 per cent. of the bentonite particles are clumped by a serum diluted 32 times or more. while it is considered to be negative when the particles remain freely suspended.

Positive results were obtained in 97 out of 114 verified cases of rheumatoid arthritis. Results were also positive in five out of eleven cases of disseminated lupus erythematosus and five out of ten scleroderma. Of 58 patients with non-rheumatic arthritis, only three gave a positive reaction. Positive results to the bentonite flocculation test were obtained in 10 per cent. of syphilitic sera as well as biological false-positive sera. *G. W. Csonka.*

Bentonite Flocculation Test in Rheumatoid Arthritis. DELTORO, R. A., SMITH, R. T., KRON, K. M., HERMANN, I. F., and CLAPPIER, M. H. (1959). *J. Amer. med. Ass.*, **169**, 315. 12 refs.

The bentonite flocculation test (see previous Abstract) was carried out on sera from 48 patients with definite rheumatoid arthritis, positive results being obtained in forty instances. A positive reaction was obtained in four out of twelve cases of probable rheumatoid arthritis, but only in three out of 35 cases of other rheumatic conditions. When the test was performed on sera from 48 patients with various diseases characterized by altered protein metabolism there was a positive reaction in one case only. It is concluded that the bentonite flocculation test is easier and cheaper to perform than other serological tests for rheumatoid arthritis and is a dependable laboratory aid in diagnosis. *G. W. Csonka.*

Colloid Osmotic Pressure of Rheumatoid Synovial Fluid. MÄKINEN, P., and KULONEN, E. (1959). *Nature (Lond.)*, **183**, 175. 3 refs.

The authors record, in abbreviated form, the results of measurements of the colloid osmotic pressure of rheumatoid synovial fluids before and after intra-articular hydrocortisone administration. This treatment was found to cause a fall in colloid osmotic pressure. Correlation with the size of the effusion was doubtful. There was positive correlation of colloid osmotic pressure with the total protein content of the fluid, and with the erythrocyte sedimentation rate, but not with the synovial fluid concentrations of sodium, potassium, chloride, hyaluronate, or with the intrinsic viscosity. It is concluded that changes in protein concentration resulting in changes in the synovial fluid colloid osmotic pressure are of importance for the formation and disappearance of the effusion. *G. Loewi.*

Purification and Isolation of Rheumatoid Factor. WILLIAMS, R. R., STEWART, L. C., and JENKINS, J. C. (1958). *Proc. Soc. exp. Biol. (N.Y.)*, **99**, 554. 7 refs.

Relative specific activities of material containing rheumatoid factor was determined by measuring inhibition of haemolytic activity of Newcastle Disease virus sensitized by the rheumatoid factor. By this technique relative specific activities of the material at successive stages of purification was determined. The method of purification consisted in dialysing the euglobulin fraction of rheumatoid plasma with diethylamino-ethyl cellulose a phosphate buffer with a pH 7·9. 93 per cent. of the activity was adsorbed. The active material was transferred to the top of a diethylamino-ethyl cellulose column for elution by stepwise increased salt and decreased pH method. The resulting active fraction was further chromatographed on carboxymethyl cellulose and yielded more than 90 per cent. of a component with a sedimentation coefficient of 18·8. The material had a sensitized sheep cell agglutination titre of 1 : 5120. Concentration dependence data for the sedimentation coefficient were determined. *G. W. Csonka.*

Alligator Erythrocyte Haemagglutination Test for the Detection of Rheumatoid Factor. COHEN, E., NETER, E., MINK, I., and NORCROSS, B. M. (1959). *Arch. interamer. Rheum.*, **2**, 75. 14 refs.

Kidney in Rheumatoid Arthritis. (Le rein dans la polyarthrite chronique évolutive.) BERTHOULD, E. (1959). *Rev. Rhum.*, **26**, 99. 6 refs.

***Post mortem* Examination of an Elderly Severe Haemophiliac, with Observations on the Pathologic Findings in Haemophiliac Joint Disease.** RODNAN, G. P., BROWER, T. D., HELLSTROM, H. R., DIDISHEIM, P., and LEWIS, J. H. (1959). *Arthr. and Rheum.*, **2**, 152. 5 figs, 19 refs.

Latex-Fixation Test in Rheumatoid Diseases with Special Regard to Rheumatoid Arthritis. Comparison with the Waaler-Rose Reaction. (Il test al lattice a goccia nelle malattie reumatiche con particolare riguardo all'artrite reumatoide. Confronto con al reazione di Waaler-Rose.) GARELLI, R. (1959). *Reumatismo*, **11**, 82. 8 refs.

Subfractions of Human Gamma Globulin as Reactant in the Latex-Fixation Test. HEDBERG, H., and MORITZ, U. (1959). *Acta rheum. scand.*, **5**, 12. 2 figs, 13 refs.

Experimental and Clinical Studies of the Antistreptolysin Reaction and the Waaler-Rose Reaction. (Experimentale und klinische Studien zur Antistreptolysinreaktion und zur Waaler-Rose-Reaktion.) SCHEIFFARTH, F. (1959). *Z. Rheumaforsch.*, **18**, 122. 3 figs, 30 refs.

Immuno-Electrophoretic Study of Rheumatoid Arthritis. (Étude immuno-électrophorétique des rhumatismes inflammatoires chroniques.) FRANCO, J.-C., EYQUEM, A., PODLIACHOUK, L., and JACQUELINE, F. (1959). *Ann. Inst. Pasteur*, **96**, 413. 13 refs.

Immunological Studies of the Activating Factor in Rheumatoid Arthritis. (Recherches immunologiques sur le facteur activateur de la polyarthrite chronique évolutive.) MOUSTARDIER, G., DULONG DE ROSNAY, C., and DU PASQUIER, P. (1959). *Ann. Inst. Pasteur*, **96**, 289. 7 refs.

Factor in Rheumatoid Arthritic Sera interfering in the Zymosan Assay of Properdin. [In English.] LAURELL, A.-B. (1959). *Acta path. microbiol. scand.*, **45**, 392. 11 refs.

Studies on the Isolation and Characterization of the "Rheumatoid Factor". KUNKEL, H. G., FRANKLIN, E. C., and MULLER-EBERHARD, H. J. (1959). *J. clin. Invest.*, **38**, 424. 9 figs, 27 refs.

Isolating the Rheumatoid Factor. SVARTZ, N. (1959). *Acta rheum. scand.*, **5**, 5. 6 figs, 7 refs.

Research into the Familial Occurrence of the Rheumatoid Factor. (Richerche sulla famigliarità del fattore reumatoide.) ROBECCHI, A., DANEO, V., EINAUDI, G., and GARELLI, R. (1959). *Reumatismo*, **11**, 66. 11 refs.

Fractionation of Urinary 17-Ketosteroids in Inflammatory Rheumatism and Gout. (Fractionnement des 17-cétostéroïdes urinaires dans les rhumatismes inflammatoires et la goutte.) JACQUELINE, F., DE TRAVERSE, P.-M., and DEPRAITÈRE, R. (1959). *Presse méd.*, 67, 505. 3 figs, 23 refs.

Bentonite Flocculation Test (BFT) in Rheumatoid Arthritis. [In English.] LAINE, V. A. I., and JULKUNEN, H. (1959). *Ann. Med. exp. Fenn.*, **37**, 100. 2 figs, 3 refs.

Studies of Heparinaemia and Heparin Tolerance in Rheumatic Fever in Childhood. (Ricerche sulla eparinemia e sulla tolleranza eparinica nella malattia reumatica dell'infanzia.) NIGRO, N. (1959). *Minerva pediat. (Torino)*, **11**, 115. 14 refs.

Contributions from Hyaluronic Acid and from Protein to the Colloid Osmotic Pressure of Human Synovial Fluid. JENSEN, C. E., and ZACHARLE, L. (1959). *Acta rheum. scand.*, **5**, 18. 5 figs, 22 refs.

Evaluation of Changes in Serum Protein in Patients with Rheumatoid Arthritis. GASPARDY, G., KOVACS, L., RAKOS, H., and VIDA, M. (1959). *Rheumatism*, **15**, 39. 9 refs.

Choline Esterase Activity in Rheumatoid Arthritis. HAMMARSTEN, G., JONSSON, E., LINDGREN, G., and NETTELBLADT, E. (1959). *Acta rheum. scand.*, **5**, 42. 4 figs, 7 refs.

Pathology of Rheumatic Fever and Rheumatoid Arthritis. (Patologie febrilního revmatismu a progressivní polyartritidy.) PAZDERKA, V. (1959). *Acta Univ. Carol., Med.*, **1**, 11. 26 figs, 56 refs.

Presence in Antibacterial Immune Sera of Anti-globulin Factors Analogous to Those of Rheumatoid Arthritis. (Présence dans les immunsérums anti-bactériens de facteurs anti-globuliniques analogues à ceux de la polyarthrite chronique évolutive.) EYQUEM, A., GUYOT-JEANNIN, A., and PODLIACHOUK, L. (1959). *Ann. Inst. Pasteur*, **96**, 295. 12 refs.

Antigenic Property of Soluble Collagen Proteins. (Antigenní vlastnost rozpustných bílkovin kolagenu.) NOVÁK, J. (1959). *Čas. Lék. čes.*, **98**, 533. 1 fig., 13 refs.

Antigenic Affinity of Soluble Collagen Proteins and Blood Serum Proteins. (Antigenní příbuznost rozpustných bílkovin kolagenu a bílkovin krevního séra.) NOVÁK, J. (1959). *Čas. Lék. čes.*, **98**, 537. 1 fig., 2 refs.

Effect of Chrysotherapy followed by Chloroquine Therapy on the Haemagglutination Titre in Rheumatoid Arthritis. (Invloed van de chrysoterapie gevolgd van chloroquinoterapie op de haemagglutinatie-reaktie in de P.C.E.) MICHOTTE, L., VANSLYPE, J., TRITSMANS, E., and VERSTRAETE, J. J. (1959). *J. belge Méd. phys. Rhum.*, **14**, 5. 13 refs.

Changes in the Size of the Lymphocytes in Rheumatoid Arthritis and Their Modification by Cortisone. (Über Veränderungen der Lymphozytengrösse bei primär chronischer Polyarthritis und ihre Beeinflussung durch Cortison.) BRAUNSTEINER, H., and SAILER, S. (1959). *Wien. Z. inn. Med.*, **40**, 1. 2 figs, 9 refs.

Connective Tissue, Histio-Capillary Unity, and Rheumatism. [In English.] BUSINCO, L. (1959). *Int. Arch. Allergy*, **14**, 295.

L.E. Phenomenon in the Tissues. (Fenomeno L.E. en los tejidos.) HERRANZ, G. (1958). *Rev. Med. Est. gen. Navarra*, **2**, 262. 13 figs, 33 refs.

Studies on the Mechanism of the Lupus Erythematosus (L.E.) Phenomenon. AISENBERG, A. C. (1959). *J. clin. Invest.*, **38**, 325. 3 figs, 26 refs.

Changes in the Blood Picture in Lupus Erythematosus, with Special Reference to the Chronic Form. (Blutbildveränderungen beim Lupus erythematodes, insbesondere der chronischen Form.) ARNDT, H. (1959). *Z. ges. inn. Med.*, **14**, 280. 6 figs, 70 refs.

Histone: an Essential Component for the Lupus Erythematosus Antinuclear Reaction. HOLBOROW, E. J., and WEIR, D. M. (1959). *Lancet*, **1**, 809. 2 figs, 9 refs.

***Para*-Toluenesulphonic Acid Test in the Diagnosis of Disseminated Lupus Erythematosus.** (Il test dell'acido para-toluensolfonico nella diagnosi di lupus eritematoso disseminato.) CORTI, L., LEGNAIOLI, M., and CONTÈ LO VULLO, L. (1958). *Settim. med.*, **46**, 487. 9 refs.

On the Serology of the L.E.-Factor. JOKINEN, E. J., and MÄKITALO, R. (1959). *Acta rheum. scand.*, **5**, 29. 3 refs.

ACTH, Cortisone, and Other Steroids

Side-effects following Triamcinolone. KENDALL, P. H., and HART, M. F. (1959). *Brit. med. J.*, **1**, 682. 1 fig., 4 refs.

The encouraging initial reports on the use of triamcinolone as a suppressive agent in rheumatoid arthritis have been followed by others suggesting that its therapeutic effect does not differ greatly from that of prednisolone. In this paper from Orpington and Farnborough Hospitals, Kent, the authors report the clinical progress and side-effects observed in 47 patients suffering from rheumatoid arthritis who were maintained on triamcinolone in doses up to 16 mg. daily for periods up to 11 months. The majority were already receiving cortisone or prednisolone for which triamcinolone was substituted because of a diminished clinical response or the appearance of side-effects. The patients were usually seen at fortnightly intervals, when a full subjective and objective assessment, together with a search for side-effects, was made, and the erythrocyte sedimentation rate and serum electrolyte levels estimated, but this was in no way a controlled trial.

In eleven of the 47 cases the drug had to be withdrawn because of rapid deterioration (seven cases) or severe side-effects (four cases). Altogether side-effects were seen in 24 cases, the commonest being facial and body flushing, which occurred in seventeen, the appearance of the face being characteristic and distinct from that seen with other steroids. Severe loss of weight occurred in seven cases and rapid symmetrical muscle wasting in four, in three of which it was predominantly in the legs. Clinical suppression of the symptoms of rheumatoid arthritis was satisfactory, and 36 patients continue to receive triamcinolone in spite of the side-effects in some cases.

It is concluded that there is little to choose between triamcinolone and prednisolone for the treatment of rheumatoid arthritis. The usual side-effects of steroid therapy are certainly not less frequent with triamcinolone and new ones have been seen to develop. The dosage suggested for long-term maintenance therapy is 6 mg. daily. *B. M. Ansell.*

Intestinal Perforation and Widespread Arteritis in Rheumatoid Arthritis during Treatment with Cortisone. PARKER, R. A., and THOMAS, P. M. (1959). *Brit. med. J.*, **1**, 540. 2 figs, 18 refs.

Three cases of intestinal perforation and widespread arteritis in rheumatoid arthritis during treatment with cortisone are described. Most of the few cases of intestinal perforation previously described in patients under treatment with cortisone have had intestinal disease. Widespread acute arteritis is rarely found in rheumatoid arthritis, but since the advent of cortisone therapy such cases appear to have increased. It is suggested that cases of rheumatoid arthritis on cortisone have a greater liability than other diseases to develop an acute arteritis.

We consider that the intestinal perforation and arteritis in the present cases are probably separate abnormal reactions to cortisone which are more likely to occur in cases of rheumatoid arthritis than in other diseases.—[*Authors' summary.*]

Clinical and Metabolic Effects of Dexamethasone. SLATER, J. D. H., HEFFRON, P. F., VERNET, A., and NABARRO, J. D. N. (1959). *Lancet*, **1**, 173. 7 figs, 10 refs.

Dexamethasone (9α-fluoro-16α-methylprednisolone) is reported to have seven and a half times the anti-inflammatory action of prednisolone. The metabolic effects of dexamethasone were studied in four cases of the nephrotic syndrome and one of acquired haemolytic anaemia seen at the Middlesex Hospital, London. In a dosage of 4 mg. a day, dexamethasone had a sodium diuretic effect, and on the first day of administration urinary excretion of potassium increased. Subsequently, excretion of nitrogen and of potassium increased progressively, and substitution of prednisone in a dosage of 40 mg. daily for dexamethasone did not alter it. Dexamethasone had no effect on the blood sugar level or the urinary excretion of glucose in healthy subjects, but the latter value was increased in a patient with diabetes. The serum calcium level and the urinary excretion of calcium increased with dexamethasone therapy. The effects of the drug in this respect appeared to be greater than those of the older steroids, and it is suggested that

it should not be given in the treatment of hypercalcaemic states. The adrenal suppressive effect of dexamethasone was quite equal to that of the older steroids in the relative doses used. In three out of the five cases of the nephrotic syndrome, there was a significant decrease in the urinary excretion of protein, accompanied in two of the cases by a rise in the plasma protein concentration. In one patient, who was oedematous, a satisfactory diuresis was obtained.

It is concluded that the increased potency of dexamethasone is of no value therapeutically unless undesirable side-effects, such as peptic ulceration, susceptibility to infection, development of osteoporosis, muscle weakness, mental changes, diabetes, and adrenal atrophy, "can be shown to be less likely". *P. A. Nasmyth.*

Plasma 17-Hydroxycorticosteroids in Patients with Certain Rheumatic Diseases and in Normal Persons. WARD, L. E., CHUNG WU, HENCH, P. S., MASON, H. L., SLOCUMB, C. H., POLLEY, H. F., and MAYNE, J. G. (1958). *Proc. Mayo Clin.*, **33**, 611. 3 figs, 43 refs.

The plasma 17-hydroxycorticosteroid level was determined at intervals during the day (8 a.m. to 6 p.m.) in 56 normal persons and in 101 patients with rheumatoid arthritis, eighteen with ankylosing spondylitis, twelve with osteo-arthritis, fourteen with gout, and eighteen with "psychogenic" rheumatism. A diurnal variation in the level was found in all groups, and only minor differences were noted between them. The level was found to be raised for some hours after an intra-articular injection of hydrocortisone in cases of rheumatoid arthritis. It is concluded that no differences in the production of 17-hydroxycorticosteroids and their utilization by the body as a whole between normal individuals and those with rheumatoid arthritis or the other conditions studied can be detected by the methods of investigation at present available, though the possibility of differences in the metabolism of these hormones by various specific tissues requires further study.

Oswald Savage.

Experience with the Prolonged Use of Prednisone and Prednisolone by the Intramuscular Route in Rheumatology. (Experiencia con el uso prolongado de prednisone y prednisolona por via intramuscular en reumatología.) SANTAMARINA, V., ROCÉS, E., LOPETÉGUI, A., and PALACÍN, A. (1958). *Arch. interamer. Rheum.*, **1**, 718.

Plasmacorticosteroids and Their Responsiveness to Corticotrophin after Long-Term Therapy with Corticosteroids and Corticotrophin. [In English.] BIERICH, J. R., KERSTEN, I., and MARUEKTAD, S. (1959). *Acta endocr. (Kbh.)*, **31**, 40. 5 figs, 11 refs.

Comparative Studies of the Effects of Hexadecadrol (Dexamethasone) and Prednisone in the Treatment of Chronic Rheumatism. (Vergleichende Untersuchungen über die Wirkung von Hexadecadrol und Prednison bei der Behandlung des chronischen Rheumatismus.) MIEHLKE, K., and THÜRIGEN, G. (1959). *Z. Rheumaforsch.*, **18**, 131. 1 fig., 5 refs.

Problems in the Corticosteroid Therapy of Rheumatic Disease. BLECHMAN, W., and VAUGHAN, J. H. (1959). *Ann. intern. Med.*, **50**, 571. 2 figs, 37 refs.

Local Injections of Hydrocortisone and Hydrocortancyl in Non-Articular Rheumatism. (Les injections locales d'hydrocortisone et d'hydrocortancyl dans les manifestations abarticulaires du rhumatisme.) JOLY, L. (1958). *Rhumatologie*, **10**, 265. Bibl.

Inflammatory Reactions to Intra-Articular Corticotherapy. A Clinical and Experimental Study. (Les réactions inflammatoires de la corticothérapie intra-articulaire. Étude clinique et expérimentale.) RUBENS-DUVAL, A., and VILLIAUMEY, J. (1959). *Rev. Rhum.*, **26**, 9. 2 figs, 15 refs.

Other General Subjects

Morbidity Survey of Rheumatism in Sydney. GARLAND, A. (1959). *Med. J. Austr.*, **1**, 190.

Under the auspices of the Australian Rheumatism Council, a survey was made of the incidence of rheumatism in Sydney. The survey was based upon interviews with householders in their own homes, and details were obtained from 1,608 males and 1,656 females. No clinical data were directly available to the investigators.

It was found that approximately one in five of the general population had suffered from rheumatic symptoms during the 12 months which preceded the investigation, but in this period only 215 of 642 sufferers had consulted a doctor. The sex incidence was about 17 per cent. for males and 22 per cent. for females. Rheumatic fever and "growing pains" had affected 1 per cent. and 7 per cent. respectively of children aged less than 15 years. Prevalence of both osteo-arthritis and rheumatoid arthritis showed an increase with age. Rheumatic diseases affected about 50 per cent. of invalid pensioners and persons who were permanently unable to work.

The accuracy of the findings depended upon the interviewing technique and interpretation of the answers of the various householders. Sometimes the answers provided insufficient data as to the nature of the disease. For instance, difficulty was encountered in assessing the percentage of cases of ankylosing spondylitis. Probably certain instances occurred in which ankylosing spondylitis and intervertebral-disk lesions were placed in the category of non-articular rheumatism.

On the assumption that the experience in Sydney is typical of Australia as a whole, it is estimated that rheumatic complaints in Australia cause an annual loss to industry of nearly a quarter of a million weeks at a cost in wages of more than two million pounds.

A. Garland.

New Pyrazol Derivative in the Treatment of Certain Rheumatic Diseases. (Un nuovo derivato pirazolica nel trattamento di alcune malattie reumatiche.) SCHIAVETTI, A., and SCHIAVETTI, L. (1958). *Minerva med. (Torino)*, **49**, 4865. 4 figs, 16 refs.

At the Institute of Rheumatology of the University of Rome, the authors treated a total of 97 patients aged 13

to 71 years with rheumatoid arthritis (21), degenerative joint changes (30), or non-articular rheumatism (46), with "osadrin", a preparation consisting of equal parts of 1:4-diphenyl-3:5-dioxypyrazolidine and dimethylaminophenyldimethylpyrazolone with the addition of procaine hydrochloride. The average daily dose was 1 ampoule by injection or four to six tablets by mouth for 10 to 40 days. [The dose contained in each ampoule or tablet is not stated.]

In a high proportion of cases a significant antirheumatic effect of the treatment was demonstrated locally by diminution of pain, muscular spasm, and exudation, and systemically by disappearance of fever and return to normal of the erythrocyte sedimentation rate. The preparation was well tolerated and there was no local tenderness after injection or gastric upset after oral administration. There was no water retention in spite of increased uric acid elimination.

The authors state that their results confirm those of German workers who have been using osadrin for well over 5 years. *Max Mayer.*

Myalgia in Bornholm Disease. WILLIAMS, W. O. (1959). *Proc. roy. Soc. Med.*, **52**, 477. 8 refs.

Conditioning Factors in the Pathogenesis of the Rheumatic State. [In English.] COBURN, A. F. (1958). *Arch. interamer. Rheum.*, **1**, 631. 1 fig., 171 refs.

Trauma and Rheumatism. GELFAND, L., and MERLISS, R. (1959). *Ann. intern. Med.*, **50**, 999. 12 refs.

Relationship of Trauma to Arthritis. TOBIN, W. J. (1959). *Amer. Surg.*, **25**, 332. 11 figs, 18 refs.

Rheumatoid Syndromes and Cancer of the Lung. (Sindromi reumatoidi e cancro del polmone.) MARTELLI, ALDO (1958). *G. Pneumol.*, **2**, 639. 17 refs.

Pseudo-Rheumatic Forms of Leukaemia. (Forme a tipo simil-reumatico della leucemia.) CAVALLO, A., and RIZZI, D. (1959). *Reumatismo*, **11**, 23. 3 figs, 32 refs.

Lesions of the Midbrain and Rheumatism. (Zweschenhirnstörungen und Rheumatismus.) KRAMMER, F. (1959). *Z. Rheumaforsch.*, **18**, 42. Bibl.

Rheumatic Fever in the Adult v. Atypical Rheumatoid Arthritis—V I P. [In English.] KELLY, LE M. C. (1958). *Arch. interamer. Rheum.*, **1**, 738.

Experimental Studies in Animals of the Antihyaluronidase Activity of Antirheumatic Drugs. (Tierexperimentelle Untersuchungen zur hyaluronidase-hemmenden Wirkung der Antirheumatika.) MATHIES, H. (1959). *Z. Rheumaforsch.*, **18**, 205. 9 figs, 3 refs.

Significance of Intestinal Disorders in Diseases of the Rheumatic Type. (Die Bedeutung von Darmstörungen für die Erkrankungen des rheumatischen Formenkreises.) KUHLMANN, F. (1959). *Z. Rheumaforsch.*, **18**, 200. 1 fig.

5- and 10-Year Follow-up Study of Rheumatic Patients. Role of Climate and Environment. SASLAW, M. S., HERNANDEZ, F. A., and RANDOLPH, H. E. (1959). *Amer. J. Cardiol.*, **3**, 754. 5 refs.

Insurance Aspects of Rheumatism. (Rheumatismus aus der Sicht des Gutachters.) TAUBE, H. (1959). *Z. Rheumaforsch.*, **18**, 187. 1 fig.

Treatment of Inflammatory Rheumatism at a Rehabilitation Centre. (Essai de traitement des rhumatismes inflammatoires en maison de rééducation.) CODREANO and BLANQUIER (1958). *Rhumatologie*, **10**, 255.

Significance and Nosological Position of "Fibrositis". (Sul significato e sulla posizione nosologica della "fibrosite".) LUCHERINI, T., and CERVINI, C. (1959). *Minerva med. (Torino)*, **50**, 1311. 6 figs, 95 refs.

Functional Myalgia and Autonomic Dysfunction. (Funktionelle muskulaere hypertonier og autonom dysfunktion.) LEINØE, L. H. (1959). *Nord. Med.*, **61**, 609. 15 refs.

CORRIGENDA

ANNALS OF THE RHEUMATIC DISEASES
(1959), **18**, 170

In the **Abstracts Section**, p. 170, col. 2, l. 25: *For* Freiberg, R. H. *read* Freiberger, R. H., joint author of a paper on "Peptic Ulcers in Rheumatoid Patients receiving Corticosteroid Therapy" (*Radiology*, 1958, **71**, 542).

Ann. rheum. Dis. (1959), **18**, 279.

FAMILIAL INCIDENCE OF RHEUMATOID ARTHRITIS

BY

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Several studies of the relatives of patients suffering from rheumatoid arthritis have shown a similar small increase in the incidence of the disease as compared with that found among the relatives of healthy controls. In most of these studies (Empire Rheumatism Council Report, 1950; Barter, 1952; Stecher, Hersh, Solomon, and Wolpaw, 1953; Miall, 1955) the information has been obtained from questionnaires, and few, if any, of the relatives have been seen. However, the most recent survey (Lawrence and Ball, 1958) differs in several respects from previous investigations. The propositi were 64 persons with rheumatoid arthritis or a positive sensitized sheep cell test (S.S.C.T.) who were found during surveys of the incidence of rheumatic disease among the population of the town of Leigh in Lancashire. Nearly a third of them had no clinical evidence of disease. 183 parents, siblings, and children of these individuals were examined clinically, radiologically, and serologically. The controls were a group of people matched for age and sex with the relatives seen, taken from a random sample of the population of Leigh. Among the relatives as a group, the incidence of clinical rheumatoid disease was 9 per cent. compared with 2 per cent. among the controls; radiological evidence of the disease was found in 7 per cent. of the relatives and 3 per cent. of the controls; a positive sheep cell test occurred in 13 per cent. of relatives and 5 per cent. of controls. These figures showed an increase in the incidence of the disease in relatives of affected persons of a similar order to that found in other studies, but a striking difference was revealed when the relatives of sero-positive and sero-negative propositi were considered separately. The increased incidence of clinical disease in both groups was twice as great among the relatives of those with both clinical disease and a positive sheep cell test (16 per cent. compared with 9 per cent. among sero-negative families). The sero-positive families had four times as much radiological evidence (12 per cent.) and serological evidence (20 per cent.) of rheumatoid disease as the controls, but among the relatives of sero-negative propositi the incidence was not increased. These results suggest that the familial factor is particularly associated with a positive sheep cell test, and that this may be the only manifestation of the disease in a significant number of persons at the time of examination.

It is recognized that the result of the sheep cell test may vary over a period of time in individual patients. In a series of 333 cases of rheumatoid arthritis observed by the authors, in whom the test had been performed on two or more occasions, the results fluctuated between positive and negative in 28 per cent.

Though hospital patients are likely to be among the most severely affected and therefore not representative of the whole pattern of the disease, it was felt that a study of the relatives of such a group, in whom the results of the sheep cell test had been consistently positive or consistently negative over a considerable period, might shed some additional light on the pattern of familial incidence revealed by the work of Lawrence and Ball.

Material

Propositi

The 63 propositi were chosen on the basis of the results of two or more sheep cell tests. All had been in-patients in the Rheumatic Unit, and all had been followed for a number of years since discharge. The sheep cell test had been consistently positive in 28 and consistently negative in 35. The composition of the group in respect of clinical severity of disease and the result of the sheep cell test is shown in Table I.

TABLE I

CLINICAL GRADING OF RHEUMATOID ARTHRITIS AND RESULTS OF SENSITIZED SHEEP CELL TEST IN PROPOSITI

Result of S.S.C.T.	Clinical Grading	Sex		Total	
		M	F		
Negative	Severe and Moderate	6	14	20	35
	Mild	8	7	15	
Positive	Severe and Moderate	8	14	22	28
	Mild	3	3	6	
Total		25	38	63	

The distribution of the propositi in respect of age and sex is shown in Table II; 35 were resident in Edinburgh, the remainder in different parts of South-East Scotland.

Relatives

The patients had 510 first-degree relatives over the age of 14 years, made up of 126 parents, 246 siblings, and 138 offspring. Of these, 238 (46 per cent.) were accessible and 202 of them agreed to undergo examination. Of the total of 510, 11·9 per cent. of parents, 41·4 per cent. of siblings, and 60·8 per cent. of offspring were seen. The composition of the group by age and sex is shown in Table III.

Method

The majority of the relatives were seen by appointment at the Unit. A history of past or present rheumatic symptoms, previous illness, or injury, and the presence or absence of morning stiffness was obtained. Joints were examined clinically, and a sample of blood was taken for estimation of haemoglobin (100 per cent. = 14·8 g./100 ml.), erythrocyte sedimentation rate, and serological examination. Radiological examination of hands, feet, and cervical spine was carried out in all cases, and if other joints appeared to be involved at the clinical examination these were also *x* rayed.

In the case of relatives examined at their homes, the haemoglobin level and erythrocyte sedimentation rate were not estimated, but blood was taken for the sheep cell test; arrangements were made for radiological examination to be carried out at local hospitals in all but two instances, men aged 82 and 85, both of whom, clinically, had mild osteo-arthrosis; both had negative sheep cell tests. Blood was not obtained from two women, aged 29 and 48, neither of whom had clinical or radiological evidence of rheumatoid disease.

The *x* rays were read by two observers, five grades being used in respect of rheumatoid arthritis, osteo-arthrosis, and disk degeneration:

0 = normal, 1 = doubtful, 2 = mild, 3 = moderate, 4 = severe.

Only Grades 2 to 4 were regarded as positive in the final analyses.

The sensitized sheep cell test was performed by the method of Ball (1950) modified by the use of M.R.C. haemagglutination plates in place of test tubes. Comparison with the results in this laboratory using Ball's original method showed that higher titres were recorded on the plates. In order to retain both the specificity and sensitivity of the original test it was considered advisable to designate a titre of 1/128 as the lowest indicating a positive result.

Results

Of the 202 people examined, 92 were relatives of patients with a consistently positive sheep cell test and 110 were relatives of patients in whom the results had always been negative.

Incidence of Rheumatic Complaints

The over-all incidence of rheumatic complaints is shown in Table IV (opposite).

Relatives of Sero-Positive Patients.—31 (33·7 per cent.) had some rheumatic complaint at the time of examination. Of these, 23 (74 per cent.) had radiological changes in the hands, feet, cervical spine, or other joints which supported the clinical diagnosis. Of the 61 relatives with no complaints, five had

TABLE II

PROPOSITI BY SEX, AGE, AND RESULTS OF SENSITIZED SHEEP CELL TEST

Sex		Male						Female					
Age (yrs)		15-34	35-44	45-54	55-64	65+	Total	15-34	35-44	45-54	55-64	65+	Total
Results of S.S.C.T.	Negative	1	3	4	3	3	14	1	4	7	8	1	21
	Positive	0	0	2	8	1	11	0	4	2	7	4	17
Total		1	3	6	11	4	25	1	8	9	15	5	38

TABLE III

AGE AND SEX OF RELATIVES OF PROPOSITI

Sex		Male							Female							Total
Age (yrs)		15-24	25-34	35-44	45-54	55-64	65+	Total	15-24	25-34	35-44	45-54	55-64	65+	Total	
Result of S.S.C.T. of Propositi	Negative	12	8	9	13	7	3	52	9	10	11	14	6	8	58	110
	Positive	3	15	6	11	5	4	44	7	8	9	8	13	3	48	92
Total		15	23	15	24	12	7	96	16	18	20	22	19	11	106	202

TABLE IV

INCIDENCE OF RHEUMATIC COMPLAINTS AMONG RELATIVES

Result of S.S.C.T. of Propositi	No. of Relatives	No Complaints or Past Complaints Only				Complaints at Time of Examination			
		No.	Per cent.	*X*-ray Signs		No.	Per cent.	*X*-ray Signs	
				No.	Per cent.			No.	Per cent.
Negative ..	110	82	74·5	15	18·3	28	25·5	17	60
Positive ..	92	61	66·3	6	9·9	31	33·7	23	74
Total ..	202	143	70·8	21	14·6	59	29·2	40	67·7

radiological evidence of mild osteo-arthrosis or of disk degeneration; one man had minimal radiological signs of rheumatoid arthritis.

Relatives of Sero-Negative Patients.—28 (25·5 per cent.) had rheumatic symptoms at the time of examination, in seventeen (60 per cent.) of whom radiological examination supported the clinical diagnosis. Fifteen of the 82 relatives with no complaints had radiological evidence of mild osteo-arthrosis or of disk degeneration.

There is no statistically significant difference between the groups ($p > 0{\cdot}2$).

Clinical Diagnosis

The diagnoses made on clinical grounds are shown in Table V.

The "undetermined" group included people with minor complaints such as tenosynovitis, capsulitis of shoulder, ligamentous strain, and ill-defined aches and pains.

Clinically osteo-arthrosis was mild in most cases in both groups; there was little more than the presence of Heberden's nodes in three cases among the sero-positive families, and in one among the sero-negative.

Rheumatoid arthritis was graded as moderate or severe in three cases in each group.

There is no statistically significant difference between the two groups as a whole ($p > 0{\cdot}1$) or in respect of the different diagnostic categories, except in the case of osteo-arthrosis which is commoner in relatives of sero-positive patients ($p = 0{\cdot}05$).

Radiological Diagnosis

The results of radiological examination are shown in Table VI.

TABLE V

CLINICAL DIAGNOSIS AMONG RELATIVES

Results of S.S.C.T. of Propositi	No. of Relatives	Undetermined		Disk Degeneration		Osteo-Arthrosis		Osteo-Arthrosis + Disk Degeneration		Rheumatoid Arthritis	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Negative ..	110	8	7·3	6	5·5	6	5·5	2	1·8	6	5·5
Positive ..	92	5	5·4	7	7·6	12	13	3	3·3	4	4·4
Total ..	202	13	6·7	13	6·7	18	8·9	5	2·4	10	4·9

TABLE VI

RADIOLOGICAL DIAGNOSIS AMONG RELATIVES

Results of S.S.C.T. of Propositi	No. of Relatives *X* rayed	Disk Degeneration		Osteo-Arthrosis		Osteo-Arthrosis + Disk Degeneration		Rheumatoid Arthritis	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Negative	110	16	14·6	5	4·5	8	7·3	3	2·7
Positive	90	12	13·3	8	8·9	5	5·5	4	4·4
Total	200	28	14	13	6·5	13	6·5	7	3·5

There is no significant difference between the groups as a whole, nor in respect of any diagnostic category ($p > 0{\cdot}1$).

Results of Sensitized Sheep Cell Test

Detailed results of the sheep cell test are shown in Table VII. Among the relatives of sero-positive patients the test was positive in four, two of whom had no clinical or radiological evidence of disease. Among relatives of sero-negative patients the test was positive in two, one of whom had no clinical or radiological evidence of disease.

There is no significant difference between the two groups.

Haemoglobin Level and Erythrocyte Sedimentation Rate

Haemoglobin level and erythrocyte sedimentation rate were estimated in 84 relatives of sero-positive patients and in 100 relatives of sero-negative patients.

Sero-Positive Group.—Five persons, all women, had a haemoglobin level below 80 per cent. None had a raised erythrocyte sedimentation rate, and the sheep cell test was negative in each case. Four had had mild rheumatic complaints in the past.

Seventeen people in this group (two men and fifteen women) had an erythrocyte sedimentation rate above 20 mm./1 hr. Three had evidence of intercurrent infection, three had rheumatoid arthritis, five had signs of generalized osteo-arthrosis and in six no cause was found. The sensitized sheep cell test was positive in two cases with clinical rheumatoid arthritis.

Sero-Negative Group.—Eight persons (seven women and one man) had a haemoglobin level below 80 per cent. In none was the sheep cell test positive and only one woman had an erythrocyte sedimentation rate above 20 mm./1 hr. Six had had mild rheumatic complaints in the past.

Thirteen people (two men and eleven women) had an erythrocyte sedimentation rate above 20 mm./1 hr; three had rheumatoid arthritis, two had signs of osteo-arthrosis, and in eight no cause was found. One person with clinical rheumatoid arthritis had a positive sensitized sheep cell test.

There is no significant difference between the groups in respect of these characteristics.

Morning Stiffness

Sero-Positive Group.—Eleven persons complained of morning stiffness; four had rheumatoid arthritis, one had generalized osteo-arthrosis with a raised erythrocyte sedimentation rate (24 mm./1 hr), one had evidence of degenerative disk lesions, four gave a history of ill-defined joint pains without objective clinical or radiological signs, and one had no rheumatic complaint. All except two people with definite rheumatoid arthritis had negative sensitized sheep cell tests.

Sero-Negative Group.—Twelve persons complained of morning stiffness; five had rheumatoid arthritis, two had generalized osteo-arthrosis with a normal erythrocyte sedimentation rate, two gave a history of mild, ill-defined, joint pains with no objective signs, one had tenosynovitis, one gave a history of backache and had a positive sensitized sheep cell test (1/128), and one had no complaints.

The incidence of this symptom does not differ significantly in the two groups.

Rheumatoid Disease

The incidence of rheumatoid disease among the relatives is shown in detail in Table VIII (opposite).

Seven people in each group had some evidence of this condition. All were siblings of the propositi; the cases came from eleven families, six in the sero-positive group and five in the sero-negative group. Their ages ranged from 35 to 61 years.

The three individuals with a positive sensitized sheep cell test as their only evidence of disease were:

(1) A woman aged 61 (titre 1/128) who gave a history of an episode of painful knees lasting several months, 3 years previously, but who had no residual clinical or radiological signs;

TABLE VII

SENSITIZED SHEEP CELL TEST BY TITRE AMONG RELATIVES

Result of S.S.C.T. of Propositi	No. of Relatives Tested	Negative				Positive				Per cent. Positive
		<1/16	1/16	1/32	1/64	1/128	1/256	1/512	1/1024	
Negative ..	109	87	12	7	1	1	0	0	1	1·8
Positive ..	91	71	12	4	0	1	0	0	3	4·4
Total ..	200	158	24	11	1	2	0	0	4	3·0

TABLE VIII

INCIDENCE OF RHEUMATOID DISEASE AMONGST RELATIVES

Result of S.S.C.T. of Propositi	No. Examined	Clinical and Radiological Signs		Clinical Signs only	Radiological Signs only	S.S.C.T. Positive Only	Total	Percentage
		S.S.C.T. Positive	S.S.C.T. Negative					
Negative ..	110	1	2	3	—	1	7	6·4
Positive ..	92	2	1	1	1	2	7	7·6
Total ..	202	3	3	4	1	3	14	6·9

(2) A man aged 60 (titre 1/1024) who had no history nor clinical or radiological signs of disease.

These two people were among the sero-positive families.

(3) A man aged 34 (titre 1/128) who complained of mild morning stiffness and gave a history of mild backache in the past but who had no objective clinical or radiological signs of disease. He was the brother of a sero-negative propositus.

The incidence of clinical, radiological, and serological evidence of disease is constant in the sero-positive group (4·4 per cent.), but in the sero-negative families the incidence of clinical evidence of disease (5·5 per cent.) is higher than that of radiological (2·7 per cent.) or serological (1·8 per cent.) signs.

Discussion

The results in the present study of relatives of patients suffering from rheumatoid arthritis show no statistically significant difference between the relatives of sero-positive and sero-negative propositi in any of the diagnostic categories considered, except in the incidence of clinical osteo-arthrosis which is higher among the sero-positive families.

The two groups of relatives are well matched for age and sex. There is a slightly higher proportion of young people than would be found in the general population, but this applies equally to both groups. The proportion of offspring is higher in the sero-positive (49 per cent.) than in the sero-negative (36 per cent.) families.

The incidence of rheumatic complaints as a whole is higher among the sero-positive families, but the difference between the two groups is not significant. There is little difference in the incidence of minor complaints or of disk lesions.

The incidence of clinical osteo-arthrosis is significantly higher among the sero-positive families, but there is little difference between the two groups in the incidence of radiological signs of osteo-arthrosis. All the people in whom a clinical diagnosis of osteo-arthrosis was made and who were *x*-rayed had definite, though usually minor, radiological signs of osteo-arthrosis and no radiological signs of rheumatoid arthritis; in all except two (titres 1/16), the result of the sensitized sheep cell test showed no agglutination in the lowest titre used (1/16). These facts, combined with the clinical picture, make it unlikely that confusion has arisen between the two conditions in these cases.

Comparison of the two groups in respect of rheumatoid disease does not show any striking difference between them. However, such differences as there are follow a similar pattern to that found by Lawrence and Ball. The incidence of clinical, radiological, and serological manifestations of the disease is the same (4·4 per cent.) among the sero-positive families, but among the sero-negative families the incidence of clinical disease (5·5 per cent.) is higher than that of radiological (2·7 per cent.) or serological (1·8 per cent.) signs. The numbers involved are so small that these differences depend on one or two people in each case, so that it is impossible to draw any significant conclusions from them.

There are certain differences between this study and that of Lawrence and Ball (1958). In particular, among the Scottish propositi there was none whose only manifestation of rheumatoid disease was a positive sensitized sheep cell test. However, the difference between the sero-positive and sero-negative families in Lancashire remains, even if the relatives of those with only a positive test are excluded from consideration. Among the relatives, the age distribution is similar among the sero-negative families in both studies, but in the Scottish study there are fewer people in the older age groups among the sero-positive families than was the case in Lancashire. Lawrence and Ball found that the incidence of a positive sheep cell test rose with age in all groups and that it was markedly higher among those over 65 in the sero-positive families (38 per cent. compared with 13 per cent. among the controls). In the present study none of the seventeen relatives over 65 had a positive sensitized sheep cell test, so that the reason for the difference in the results is not likely to lie in the age distribution of the families.

It is impossible at present to offer a satisfactory explanation for the difference between the results of this investigation and that of Lawrence and Ball, but it is of interest to note that in Lancashire the incidence of a positive sensitized sheep cell test is higher than that of signs of clinical disease, both in the control population and among the relatives, whereas among the Scottish families the reverse is true. 4·9 per cent. have clinical rheumatoid arthritis and 3 per cent. have a positive sheep cell test. It is known that the incidence of a positive sensitized sheep cell test may vary in different populations (Lawrence, 1959) and it is possible that this variation may influence the familial pattern of the disease.

Summary

(1) 202 relatives (parents, siblings, and children) of 63 patients suffering from rheumatoid arthritis, in whom the results of the sensitized sheep cell test had been consistently positive or consistently negative, were examined clinically, radiologically, and serologically.

(2) Clinical, radiological, or serological evidence of rheumatoid arthritis was found in 7·6 per cent. of the relatives of patients with a positive sheep cell test and in 6·4 per cent. of relatives of those with a negative test. The incidence of each kind of evidence was equal (4·4 per cent.) among the sero-positive families, but the incidence of clinical disease (5·5 per cent.) was higher among the sero-negative families than that of radiological (2·7 per cent.) or serological (1·8 per cent.) signs.

(3) No significant difference was found between the two groups in respect of haemoglobin level, erythrocyte sedimentation rate, morning stiffness, or the radiological or clinical evidence of other rheumatic complaints, except in the case of clinical osteo-arthrosis which was seen more frequently in the sero-positive families.

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We wish to express our thanks to Dr. P. Aitken for radiological assistance, Mr. S. A. Sklaroff for statistical advice, Mrs. E. Greenhill and Miss N. Lawson for their skilled technical work, and to the relatives of our patients for their co-operation.

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Fréquence familiale de l'arthrite rhumatismale

RÉSUMÉ

(1) 202 parents (ascendants, descendants et latéraux directs) de 63 malades atteints d'arthrite rhumatismale, chez qui la réaction d'agglutination des globules rouges sensibilisées de mouton avait été régulièrement positive ou régulièrement négative, furent examinés du point de vu clinique, radiologique et sérologique.

(2) Signes cliniques, radiologiques et sérologiques d'arthrite rhumatismale furent trouvés chez 7,6% des parents des malades à réaction d'agglutination positive et chez 6,4% des parents des malades à réaction d'agglutination négative. La fréquence des signes de chaque type fut égale (4,4%) dans les familles séro-positives, mais la fréquence de la maladie clinique (5,5%) fut plus grande que celle des signes radiologiques (2,7%) ou sérologiques (1,8%) dans les familles séro-négatives.

(3) On ne trouva pas de différence appréciable entre les deux groupes en ce qui concerne le taux d'hémoglobine, vitesse de sédimentation globulaire, enraidissement matinal ou des signes radiologiques ou cliniques d'autres maladies rhumatismales, sauf dans les cas d'ostéo-arthrose clinique, rencontrée plus souvent dans des familles séro-positives.

Incidencia familial de la artritis reumatoide

SUMARIO

(1) 202 parientes (padres, hermanos e hijos) de 63 enfermos con artritis reumatoide, en los cuales la reacción de aglutinación de eritrocitos sensibilizados de carnero fué sistemáticamente positiva o sistemáticamente negativa, fueron examinados clínica, radiológica y serológicamente.

(2) Signos clínicos, radiológicos y serológicos de artritis reumatoide fueron encontrados en un 7,6% de parientes de los enfermos con reacción de aglutinación positiva y en un 6,4% de parientes de los enfermos con reacción de aglutinación negativa. La frecuencia de cada tipo de signos fué igual (4,4%) en las familias seropositivas, pero la frecuencia de la enfermedad clínica (5,5%) en las familias sero-negativas fué mayor que la de signos radiológicos (2,7%) o serológicos (1,8%).

(3) No se encontró diferencia apreciable entre los dos grupos en las cifras de hemoglobina, velocidad de sedimentación eritrocitaria, rigidez matinal o signos radiológicos o clínicos de otras enfermedades reumatoides, con excepción de ósteo-artrosis clínica, encontrada más a menudo en familias sero-positivas.

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ACUTE RHEUMATIC FEVER IN YOUNG MEN

A CLINICAL AND EPIDEMIOLOGICAL STUDY

BY

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AND

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Since the turn of the century, acute rheumatic fever has become increasingly uncommon (Glover, 1930; Hitchens, 1956). Penicillin treatment of upper respiratory tract infections and the increasing use of antibiotic prophylaxis have contributed to this decline in recent years, but improved social and economic conditions and the changing pattern of streptococcal illness are probably more important. Nevertheless, rheumatic fever remains a serious problem which may become a menace during epidemics of streptococcal infection (Coburn and Young, 1949; Winblad, Malmros, and Wilander, 1947). Leff (1956) estimates that 4,000-5,000 school children in England suffer from an attack of acute rheumatic fever each year, and Knowelden (1949) has shown that the mortality from rheumatic heart disease has not paralleled the declining mortality from acute rheumatic fever, particularly in adults.

Epidemics of streptococcal infection are particularly common in institutions, so that rheumatic fever would be expected more often than in the general population. The barrack conditions of Army units in the United Kingdom form typical closed communities which provide epidemiological information not readily available from civilian sources.

This paper describes a clinical and epidemiological study in young soldiers, which was undertaken to ascertain the incidence of initial and recurrent attacks of acute rheumatic fever (as diagnosed by predetermined criteria); the pattern, frequency, and persistence of heart damage; and the importance of the preceding upper respiratory tract infection. Epidemiological data, based on the notification rate of rheumatic fever in the Army, has already been reported (Rosenbaum and Slater, 1957) and the present investigation extends this, using strict criteria for the diagnosis of the disease.

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Material

Information was obtained from or about 379 soldiers who had suffered from an attack of acute rheumatic fever while in the army. 90 per cent. of the patients were 17 to 21 years of age (mean 18·8 yrs) and all except three were under 30 years old. 51 unselected, consecutive cases were treated by one of us between 1954-56 from the day of admission to the Cambridge Military Hospital, Aldershot, to the time of their final discharge from hospital between 3 and 5 months later. Clinical data concerning a further 67 patients was obtained from consecutive case records of patients suffering from acute rheumatic fever at the Cambridge Military Hospital in 1953. These records were full and carefully kept. The clinical features of these patients (including the frequency and pattern of cardiac lesions) were similar to those present in the patients seen personally, and their treatment had been substantially the same. Therefore, both groups of patients will be considered together. The data concerning the pattern and frequency of heart lesions is derived from the 51 cases seen personally, plus the first thirty consecutive case records analysed.

Information about the remaining 261 patients was obtained by examining the official medical documents at the War Office (AMD Statistics) of all men who had been notified as suffering from acute rheumatic fever in 1952, and all those reported as suffering from acute rheumatic fever with heart involvement in 1953. The relevant information was available as an official copy of the in-patient case record, the report of the Medical Board proceedings on the patient's discharge from the Army, and a copy of the original medical data made out when the man had first joined the Army.

A total of 1,179 soldiers aged 17 to 22 were questioned personally to assess the frequency of a past attack of acute rheumatic fever in the general military population from which our patients were derived.

The criteria for the diagnosis of acute rheumatic fever was based on those of Duckett Jones (1944) and were similar to the criteria used in the Anglo-American therapeutic trial (1955). Rheumatic manifestations were divided into five major and five minor criteria. For a diagnosis of acute rheumatic fever, two major, or one

major and two minor criteria had to be present at some time during the patient's illness. The major criteria were carditis (see below), polyarthritis (see below), chorea, subcutaneous nodules, and erythema marginatum. The last three features are rare (1 to 2 per cent.) in this age group, so that carditis and polyarthritis were the only major criteria actually used. The minor criteria were fever (oral temperature above 99·3° F. on two or more occasions in 24 hours, or above 100·3° F. on any one occasion), an erythrocyte sedimentation rate of over 20 mm./hr (Westergren), a prolonged P-R interval (over 0·22 sec.) on the electrocardiogram, a definite history of acute febrile sore throat within the preceding 35 days, and a reliable history of past rheumatic fever and/or chorea *or* evidence of pre-existing *rheumatic* heart disease. Carditis was diagnosed and used as a major criterion if one or more of the following features were present: pericarditis (pericardial friction rub, pericardial effusion, or electrocardiographic changes diagnostic of pericarditis); the development of apical or basal diastolic murmurs (or, if present on admission, their subsequent disappearance); the development or change of an apical systolic murmur (by two or more grades, similar to those described in the Anglo-American trial, 1955); the development of Wenkebach A-V block or a wandering pacemaker confirmed by electrocardiography. None of our patients developed cardiac failure and a change in heart size was never used as the only evidence of carditis. Only one patient had evidence of old rheumatic heart disease on admission.

Polyarthritis meant pain on movement, and tenderness, swelling, redness, and heat of the affected joints. All the patients had these signs in more than one joint except for one man whose arthritis was monarticular. However, this patient also had prolongation of the P-R interval on the electrocardiogram. Multiple joint pains in the absence of objective changes and a monarticular arthritis without carditis were not accepted as criteria for diagnosis.

A diagnosis of a past attack of rheumatic fever was only accepted if the man had been in bed for at least 6 weeks and if two or more joints had been painful and swollen at some time during the illness.

In the classification of the cardiac lesions, the following terms need explanation: a *persistent lesion* is defined as one which persists until the patient's final discharge from hospital (the time that a patient spends in hospital naturally varies greatly, but the average was 5 months with a range of 3 to 10 months); an *abnormal murmur* means either the development of an apical or basal diastolic murmur or a change in intensity of an apical systolic murmur by two or more grades (see above); *abnormal electrocardiographic changes* mean either a prolonged P-R interval, other evidence of an atrioventricular block, or evidence of a localized pericarditis; *pericarditis* means either a pericardial friction rub or a pericardial effusion or both.

Methods

Assessment of the progress of the 51 patients cared for by one of us (J.D.H.S.) was made by recording all relevant clinical and pathological findings on a specially prepared chart. Daily physical examination was made during the acute stage of the disease, particular attention being paid to the state of the heart. Electrocardiographic tracings were taken on admission, and then at standard intervals (alternate days for 8 days and weekly thereafter) as well as when clinically indicated. After the acute stage, clinical and electrocardiographic assessment was made at 1 to 2 weekly intervals.

The patients were treated with rest in bed, salicylates, and penicillin. The duration of the rest in bed and the rate of subsequent mobilization was carried out according to a standard schedule, which, in the absence of clinical evidence of continuing rheumatic activity, depended chiefly upon the behaviour of the erythrocyte sedimentation rate (Westergren). Salicylate was given as aspirin tablets in sufficient amounts to procure plasma salicylate levels of at least 30 mg. per 100 ml. 2 hours after the last dose. These were estimated weekly. Penicillin (procaine penicillin 500,000 units twice daily intramuscularly) was given to all cases for the first 10 days and prophylaxis against further streptococcal infections was secured by 0·5 g. sulphadimidine twice daily for the rest of the patient's stay in the Army. Treatment was started within 48 hrs of the onset of symptoms in 45 per cent. of cases, and within 7 days in all patients except two who had been ill for 10 and 14 days respectively.

Results

Annual Incidence of Rheumatic Fever.—Table I shows the yearly frequency of acute rheumatic fever notifications in the military population of the United Kingdom from 1947 to 1954. During this period of time there has not been any detectable decline in the official returns for the disease, the average figure being 1·10 per 1,000 per year. However, more detailed analysis of the records for 1952 and 1953 showed that in 57 (22 per cent.) the reported diagnosis had to be discarded: 36 may have had mild rheumatic fever but our diagnostic criteria were not satisfied, ten had old rheumatic heart disease, and the rest past rheumatic fever, idiopathic pericarditis, bacterial endocarditis, or the effort syndrome. This

TABLE I

REPORTED YEARLY INCIDENCE OF RHEUMATIC FEVER NOTIFICATION IN THE BRITISH ARMY

Year	Reported Attack Rate per 1,000
1947	0·9
1948	0·8
1949	0·8
1950	1·2
1951	0·9
1952	1·3
1953	1·7
1954	1·0
Average	1·1

makes the incidence of the disease, as defined by our criteria, 1·01 per 1,000 for all attacks and 0·70 per 1,000 for first attacks. Applying a similar correction factor to the reported annual attack rate for 1947-54, the incidence of acute rheumatic fever (as defined) is about 0·85 per 1,000 or 0·59 per 1,000 for first attacks.

Distribution of Rheumatic Fever Attacks according to Length of Service.—The majority of attacks occur within 6 months of enlistment and there is a 1 to 2-month delay before the peak is reached (Figure). This is true for both initial and recurrent attacks. By contrast, the distribution of admissions for all other diseases is at a maximum during the first month of military service and then falls off progressively. The subsequent fall in the number of rheumatic fever attacks begins before the usual period of training in the country is complete, although some of the decline from the fourth month onwards may be explained by postings overseas where rheumatic fever is less commonly notified.

Frequency of a Previous Attack in Patients with Rheumatic Fever.—Table II shows that 31 per cent. of the 118 patients seen at the Cambridge Military Hospital had a past history of rheumatic fever by our criteria.

TABLE II

FREQUENCY OF PAST RHEUMATIC FEVER IN 118 RHEUMATIC FEVER PATIENTS

Source of material	No. of Cases	Past Rheumatic Fever	
		Definite	Possible
Case Notes ..	67	21 (31 per cent.)	5
Personal Series ..	51	16 (31 per cent.)	13

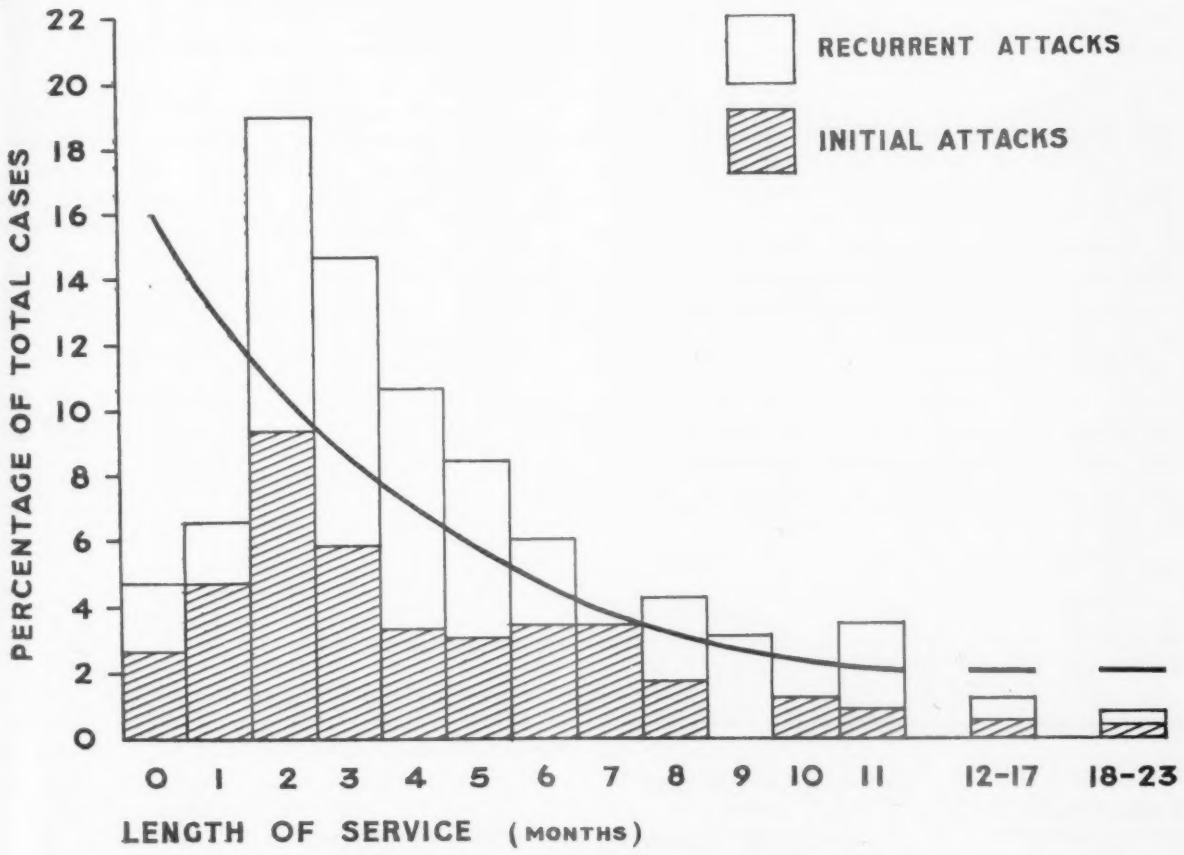

Figure.—Distribution of cases of rheumatic fever by length of service.
Black line (———) shows smoothed trend of hospital admissions for all diseases (U.K.).

The relevant information was available in only 119 of the 203 official records which remained after discarding the cases which did not satisfy our criteria (Table III). This means that the proportion of cases with a past history of rheumatic fever is almost certainly too high because of the natural tendency to record only positive findings. Even including the cases in which a past history of the disease was not mentioned, the proportion is 22 per cent., so that the true value lies between this and 39 per cent. which agrees with the figure of 31 per cent. obtained directly from the patients.

TABLE III

FREQUENCY OF PAST RHEUMATIC FEVER IN THE OFFICIAL MEDICAL RECORDS OF RHEUMATIC FEVER PATIENTS

Past Rheumatic Fever	No. of Cases	Past Rheumatic Fever	
		No.	Per cent.
Mentioned	119	46	39
Not Mentioned	84	—	
Total	203	46	23

Time Interval since the Previous Attack in Patients with Recurrent Rheumatic Fever.—Table IV shows the length of time since the last attack in 35 patients seen at the Cambridge Military Hospital. 74 per cent. had had their last attack over 5 years previously. In contrast, among 22 patients admitted with possible mild rheumatic fever who gave a past history of the disease but who did not fulfil our criteria, only 36 per cent. had had their previous attack over 5 years beforehand.

TABLE IV

YEARS SINCE THE LAST ATTACK IN 57 PATIENTS WITH DEFINITE OR DUBIOUS RECURRENT RHEUMATIC FEVER

Years since Last Attack	Diagnosis			
	Certain		Dubious	
	No.	Per cent.	No.	Per cent.
Within 5	9	26	14	64
Over 5	26	74	8	36
Total	35	100	22	100

Frequency of a Past Attack of Rheumatic Fever in Young Healthy Soldiers.—Table V shows that 1·02 per cent. of 1,179 variously collected young soldiers had suffered from an attack of definite rheumatic fever in the past.

TABLE V

FREQUENCY OF A PAST ATTACK OF RHEUMATIC FEVER IN HEALTHY SOLDIERS AND PATIENTS WITHOUT RHEUMATIC FEVER

Source of Material	No. of Cases	Past Rheumatic Fever			
		Definite	Probable	Total	
				No.	Per cent.
Surgical Patients in Hospital	175	4	0	4	2·3
Recruits' Depot R.A.M.C.	403	3	2	5	1·2
Recruits' Depot, R.M.P. ..	181	1	0	1	0·5
Cases of Sore Throat ..	235	3	1	4	1·7
Contacts of Sore Throat Cases	185	1	2	3	1·6
Total	1,179	12 (1·02 per cent.)	5	17	1·4

Preceding Upper Respiratory Tract Infection.—Table VI gives details of the preceding throat infection in 81 consecutive, unselected cases of rheumatic fever. 55 (68 per cent.) had had a sore throat within the previous 35 days, although it was so mild in eighteen that the patient did not report sick because of it. Group A β-haemolytic streptococci were isolated from the throat in 49 (60 per cent.) on admission. This figure refers to the isolations resulting from inoculating a blood-agar plate and incubating aerobically and anaerobically overnight. Although only 55 patients (68 per cent.) had suffered from a noticeable sore throat within the preceding 35 days, a further twelve were harbouring Group A streptococci in the throat; in other words, evidence of a preceding throat infection was obtained from 67 (83 per cent. of the 81 patients).

TABLE VI

THROAT IN 81 CASES OF ACUTE RHEUMATIC FEVER

Group-A Streptococci		Isolated	*Not* Isolated	Total	
				No.	Per cent
Preceding Sore Throat	Yes	37	18	55	68
	No	12	14	26	32
Total		49 (60 per cent.)	32 (40 per cent)	81	100

Frequency and Pattern of Heart Involvement.—Out of 81 young men with acute rheumatic fever, 25 (31 per cent.) showed clinical or electrocardiographic evidence of active cardiac damage as defined by our criteria. An abnormal murmur appeared or disappeared in thirteen (16 per cent.) patients, ten of whom also showed other evidence of active carditis. Nine patients (11 per cent.)

developed persistent cardiac lesions which consisted of abnormal murmurs in all except one patient. Table VII shows the types of heart involvement encountered. Pericarditis was seen in twelve (15 per cent.) patients, a basal diastolic murmur developed in eleven, an apical systolic murmur in five, and an apical diastolic murmur in six. Only fourteen (17 per cent.) patients showed electrocardiographic abnormalities (the P-R interval was normal in the 56 cases without carditis and in the 31 patients seen over the same period of time who were suspected of having mild rheumatic fever but who did not fulfil our diagnostic criteria). In fourteen patients the diagnosis of acute carditis was based in a single abnormal finding; a prolonged P-R interval in six, a pericardial friction rub in three; and, an apical or basal diastolic murmur, Wenkebach A-V block, and a wandering pace-maker in each of the remaining five patients. A significant apical systolic murmur was never the only evidence of carditis.

TABLE VII

NEW HEART LESIONS IN 81 CASES OF ACUTE RHEUMATIC FEVER

Lesion	No. of Patients	Comment
Pericarditis	12	Pericardial friction rub 6 Pericardial effusion 3 Electrocardiograph changes only 3
Basal Diastolic Murmur ..	11	Transient 6 Persistent 5
Apical Systolic Murmur ..	5	All persistent
Apical Diastolic Murmur ..	6	Transient 3 Persistent 3
Electrocardiograph Changes ..	11	Prolonged P-R (<0·22 sec.) 8 Wenkebach A-V block 2 Wandering pace-maker 1

In Table VIII, the pattern of the heart lesions seen is compared in patients with first attacks and those with recurrent attacks of rheumatic fever. 16 per cent. of patients who had had the disease before developed persistent heart lesions, whereas only 8 per cent. of patients suffering from their first attack did so. However, this difference is not statistically significant. But, when the number of fresh abnormal murmurs which persist is compared in the two groups (Table IX), ten of twelve such murmurs persisted in patients with recurrent rheumatic fever compared with three out of ten in patients suffering from their first attack. This difference is significant statistically.

TABLE IX

PERSISTENT AND TRANSIENT ABNORMAL MURMURS IN PATIENTS WITH INITIAL AND RECURRENT ATTACKS OF ACUTE RHEUMATIC FEVER

Attacks of Acute Rheumatic Fever	No. of New Abnormal Murmurs	No. of New Abnormal Murmurs which Persist
First (15 patients).. ..	10	3
Recurrent (10 patients) ..	12	10

Discussion

In answer to the question how commonly rheumatic fever develops in young men living as a community, our results show that the average frequency of first attacks of definite rheumatic fever is about 0·59 per 1,000 per year. This figure for initial attacks, rather than the value obtained for the total number of cases seen (0·85 per 1,000 per year), provides a valid estimate of the current incidence of rheumatic fever under the conditions prevailing at the time of the study. It is slightly lower than the figure of 0·69 per 1,000 per year reported by Hewitt and Stewart (1952) for school children aged 5 to 15 years in the period 1947-51, although it is more than double the finding of Leff (1956) for children aged 0 to 14 years in the years 1951-53. Even in the 1930s, when rheumatic fever

TABLE VIII

PATTERN OF CARDITIS IN INITIAL AND RECURRENT ATTACKS OF ACUTE RHEUMATIC FEVER

Attacks of Acute Rheumatic Fever			First (50)	Recurrent (31)	Total (81)
No. of Patients with Carditis			15	10	25
Lesions	Persistent	Abnormal murmurs	3	5	8
		Electrocardiograph changes only ..	1	0	1
		Total	4	5	9
	Transient	Abnormal murmurs	4	1	5
		Electrocardiograph changes only ..	5	3	8
		Pericarditis only	2	1	3
		Total	11	5	16

was more common, only a small proportion of first attacks occurred in children over the age of 12 (Wilson, 1940), so that the incidence that we found suggests that a young man is exposed to a special risk of rheumatic fever under service conditions in England. This is not proof, however, because an adequate civilian control group cannot be assembled. Unless there is some particular (usually medical) reason, all young men between 17 and 21 years of age are enlisted in one of the military services. Therefore we looked for variations of incidence within the Army in England, and Fig. 1 shows that susceptible individuals contract rheumatic fever within the first few months of community living, which provides independent evidence that service conditions increase the risk of rheumatic fever.

Why this should be is more difficult to explain. The prevention of rheumatic fever by prophylaxis against streptococcal infections (Thomas and France, 1939; Wannamaker, Rammelkamp, Denny, Brink, Houser, Hahn, and Dingle, 1951; Houser, Eckhardt, Hahn, Denny, Wannamaker, and Rammelkamp, 1953) provides the most compelling evidence that Lancefield Group-A streptococci are necessary for the development of the disease. Serum anti-streptolysin-O estimations were not performed in our patients, but 60 per cent. were harbouring streptococci in the throat and evidence of a preceding throat infection was obtained from a total of 83 per cent. This agrees with the figures obtained from other series (McCarty, 1952).

However, using material from a similar population, Brumfitt, O'Grady, and Slater (1959) have found that although Group-A streptococci are often isolated from patients with endemic acute sore throat, subsequent rheumatic fever is rare compared with the figure of about 3 per cent. which has been widely quoted from the evidence of Rammelkamp, Denny, and Wannamaker (1952) in young American airmen. The British workers suggest that a benign form of "streptococcal" sore throat may exist endemically in which the streptococcus plays an opportunist role. In epidemics of acute sore throat the rheumatic fever attack rate may rise as high as 10-16 per cent. (Paul, 1943; Winblad and others, 1947) and, under these conditions, actual invasion of the pharyngeal tissues by streptococci probably occurs. Although small, unnoticed epidemics of genuine streptococcal infection cannot be excluded in the present study, it would seem that some other factor apart from the presence of Lancefield Group-A streptococci is necessary to explain the relatively high incidence of first attacks of rheumatic fever among military recruits in England. This is in keeping with the results of Saslaw and Streitfeld (1956), who found no cases of rheumatic fever in a large number of school children with clear evidence of Group-A streptococcal infection.

The effect of a previous attack of rheumatic fever on the risk of recurrence when young men live as a community is well shown by our figures. We have found that about 0·85 per 1,000 soldiers develop rheumatic fever annually. Assuming a military strength of 430,000, an average of about 366 cases of rheumatic fever occurs each year. Of these, 110 (30 per cent.) will have had a previous attack. But there are only about 4,300 (10 per 1,000) healthy soldiers who have had the disease before, so that the incidence of acute rheumatic fever in these men is 1 in 39. By contrast, of the remaining 425,700 soldiers who have never had rheumatic fever before, 256 develop the disease; an incidence of 1 in 1,663. Therefore a young man who has already suffered from an attack of rheumatic fever in childhood which was sufficiently mild to leave his heart unscathed is about 42 times more likely to succumb to another attack than his more fortunate colleague who has never suffered from the disease. This emphasizes the need to advise patients with rheumatic fever to avoid institutional life. From the purely military point of view, by exempting 1 to 1·5 per cent. of recruits because of past rheumatic fever, or by enforcing continuous prophylaxis, about a third of the total number of cases in the Army could be prevented. The importance of this is brought out by our finding that persistent cardiac damage in young men with previously normal hearts is more common after a recurrence of rheumatic fever than after a first attack.

Over 70 per cent. of our patients with a past history of rheumatic fever had had their last (and usually only) attack over 5 years previously. Despite this long interval, increased susceptibility appears to persist into adult life. The duration of continuous prophylaxis with penicillin or sulphonamides following rheumatic fever in childhood is still a matter of opinion (American Heart Association, 1955; Royal College of Physicians Rheumatic Fever Committee, 1957), but it would appear that in England protection is still required in early adult life if the patient is exposed to an environment which increases the risk of rheumatic fever, however long before the last attack of rheumatic fever had occurred. This agrees with the findings of Bywaters and Thomas (1958), who state that "there is manifestly no great falling off of recurrence rates after puberty". Treatment of acute streptococcal sore throat with courses of penicillin long enough to eradicate the streptococcus (Wannamaker, Denny, Perry, Rammelkamp, Eckhardt, Houser, and Hahn, 1953; Brumfitt and

Slater, 1957), will considerably reduce the risk of clinically manifest rheumatic fever (Catanzaro, Stetson, Morris, Chamavitz, Rammelkamp, Stolzer, and Perry, 1954), but Weinstein, Boyer, and Goldfield (1955) have shown that, in children, the incidence of rheumatic heart disease following the penicillin treatment of scarlet fever is probably little different from that in untreated patients. This emphasizes how important it is to prevent streptococcal infections rather than to treat them with penicillin as they arise.

Cardiac manifestations in acute rheumatic fever are difficult to compare precisely with other series because they depend so largely on subjective findings. The varying interpretations of the significance of apical systolic murmurs, the difficulties of hearing soft diastolic murmurs, and the confusion between an apical diastolic murmur and a normal third heart sound are well shown in recent reports (Anglo-American trial, 1955; Lazar, Maas, Lipscomb, Hammond, and Rantz, 1957). Nevertheless, the similarity of the incidence of significant, not previously recorded, murmurs in our patients (16 per cent.) with that described by Lazar and others (1957) in young American airmen (19 per cent.) is probably not fortuitous, because the patients were comparable in other respects. Cardiac involvement is well known to be much more common in children than in adults, but it is interesting that the incidence of persistent heart murmurs in our patients (11 per cent.) is similar to the incidence of 1 in 8 described in the Anglo-American trial (1955) for the group of children under 16 who resembled our cases most closely (cardiac group A); and it may be that the important factor which leads to heart damage is the recurrent attack of rheumatic fever rather than age. Of course, a period of follow-up of 3 to 5 months is not long enough to be sure that patients without evidence of heart damage at the time of the acute attack will not subsequently develop cardiac murmurs, but the work of Engelman, Hollister, and Kolb (1954) showed that, among young men with rheumatic fever, abnormal murmurs present at the end of the acute attack were still present in 88 per cent. after 5 to 8 years, whereas patients without clinical carditis during the acute attack were still without abnormal murmurs at the follow-up examination.

Summary

An analysis is described of clinical and epidemiological data from 379 young men with acute rheumatic fever in the British Army.

The incidence of first attacks of the disease is about 0·59 per 1,000 per year. A previous attack increases the risk about 42 times.

Evidence is presented which suggests that institutional living carries a special risk of rheumatic fever which cannot be adequately explained by greater contact with haemolytic streptococci.

New heart lesions were seen in 31 per cent. Persistent murmurs developed in 11 per cent., being particularly common in patients who had had a previous attack.

We wish to thank Brigadier W. R. M. Drew, C.B.E., Colonel A. N. B. Odbert, O.B.E., Colonel W. R. C. Spicer, Colonel J. A. G. Carmichael, and Lieut.-Colonel R. M. Johnstone, M.B.E., M.C., whose constant co-operation made this work possible.

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Rhumatisme articulaire aigu des jeunes gens—étude clinique et épidémiologique

RÉSUMÉ

On présente une analyse clinique et épidémiologique des données concernant 379 jeunes gens de l'Armée Britannique atteints de rhumatisme articulaire aigu.

La fréquence de la première atteinte de cette maladie est à peu près 0,59 par 1000 par an. Une attaque antérieure en fait augmenter le risque 42 fois environ.

On présente des données suggérant qu'une vie communale implique un risque spécial de rhumatisme articulaire aigu, qu'un contact plus fréquent avec le streptocoque hémolytique n'explique pas suffisamment.

Des lésions cardiaques récentes furent observées dans 31% des cas. Des souffles persistants apparurent dans 11% des cas, particulièrement chez des malades ayant subi une attaque antérieure.

Reumatismo poliarticular agudo en el joven—estudio clinico y epidemiológico

SUMARIO

Se presenta un análisis clínico y epidemiológico de datos sobre 379 jóvenes del Ejército Británico afectos de reumatismo poliarticular agudo.

La frecuencia del primer ataque de esta enfermedad es cerca de 0,59 por mil por año. Un ataque anterior hace aumentar el riesgo 42 veces aproximadamente.

Se presentan datos indicando que una vida comunal implica un riesgo especial de reumatismo poliarticular agudo; un contacto más frecuente con el estreptococo hemolítico no basta para explicar este riesgo.

Lesiones cardiacas recientes fueron observadas en un 31% de los casos. Soplos persistentes aparecieron en un 11% de los casos, particularmente en enfermos con ataques previos.

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DIFFERENCES BETWEEN THE FEVER OF STILL'S DISEASE AND THAT OF RHEUMATIC FEVER

BY

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In the last 12 years' observation of a series of over 1,000 cases of rheumatic fever, over 200 cases of Still's disease, and other less common "connective tissue diseases" in children, we have come to place some diagnostic value on the character of the fever. Our impression has been that, in Still's disease, and, much less commonly, in a few cases of adult rheumatoid arthritis, the body temperature chart shows a large daily swing, reaching high levels at night and coming down to below 98·4° F. by morning, often over prolonged periods, whereas in rheumatic fever the temperature, though equally high, is more stable and shows much less swing. However, there seem to be many exceptions to this general impression and we have therefore undertaken a detailed survey of this question.

Material

The charts of all patients diagnosed as having Still's disease up to the age of 16 at the time of admission were surveyed and all cases were selected who showed a period of fever (as defined below) during one week of their hospital admission, when they were not receiving anti-pyretic treatment. Fifty cases were thus selected out of a total of something over 200. From the patients with rheumatic fever admitted over the same period, the middle 4-year intake was surveyed and fifty cases were chosen in the same way, *i.e.* these cases showed fever (as defined below) while being treated with bed rest alone without specific anti-pyretic drugs for a period of at least one week. This was possible because during this time the effects of bed rest alone in rheumatic fever were being studied. In each instance, no salicylate or steroid therapy had been given for at least 4 days before the study and none was given during the period of study. In some children, codeine phosphate was administered when needed to control pain.

For the purpose of this study, fever was defined as an oral temperature record of 99·4° F. or more on two occasions in the 7 days, or of 100·4° F. on one or more occasions. Temperatures were read by the nursing staff to an accuracy of 0·2° F. at 4-hourly intervals during periods of fever. The thermometers had previously been checked in the laboratory.

All cases in the rheumatic fever group satisfied the criteria set up by the American Heart Association, *viz.*: one major and two minor manifestations, listed as follows:

Major	*Minor*
Carditis	Fever
Polyarthritis	Elevated sedimentation rate
Chorea	Increased P-R interval
Nodules	Evidence of recent streptococcal infection
Erythema marginatum	Reliable history of rheumatic fever or evidence of pre-existing rheumatic heart disease.

All such patients were between the ages of 4 and 16. Still's disease was defined as a chronic polyarthritis with onset below the age of 16 years without evidence of other disease, such as tuberculosis, ankylosing spondylitis, disseminated lupus erythematosus, or ulcerative colitis, on their follow-up record. Arthritis was considered to be present if any two of the following triad were present: pain, swelling, or limitation of movement.

Of the group with Still's disease 47 patients filled these criteria, and three were cases of monarticular arthritis in which the diagnosis was established as the result of joint biopsy. The children were all aged between 2 and 16 years at the time of study.

During the 7-day period of maximal fever, which was usually within the first week of hospital admission, estimates were made for each case of the

maximum daily swing in temperature during the week, the mean maximum and minimum daily temperatures over a period of one week, the maximum temperature reached during the week, and the general pattern of the temperature chart. Erythrocyte sedimentation rates were estimated during this week by the Westergren method and correlation made with temperature.

Results

The results are given in Tables I, II, and III. The maximum temperature during the week, the maximum daily swing of temperature for each case during

TABLE III

MEAN HIGHEST INDIVIDUAL TEMPERATURE DURING THE WEEK

Erythrocyte Sedimentation Rate (mm./hr)	Body Temperature (° F.)	
	Still's Disease	Rheumatic Fever
0–50	101·9	100·7
51–100	102·6	101·5
100+	101·4	102·4
Total	102·3±1·63° F.	101·4±1·31

$$C = \frac{0{\cdot}9}{0{\cdot}24} = 3{\cdot}75 \qquad P = <0{\cdot}001$$

TABLE I

MEAN MAXIMUM DAILY SWING DURING ONE WEEK IN JUVENILE RHEUMATOID ARTHRITIS AND RHEUMATIC FEVER

Condition	Erythrocyte Sedimentation Rate (mm./hr)	No. of Cases	Body Temperature (° F.)		
			Highest	Lowest	Difference
Still's Disease	0–50	10	101·5	98·1	3·4
	51–100	31	102·3	98·5	3·8
	100+	9	101·0	97·9	3·1
	Total	50	101·9	98·3	3·6
					S.E. 1·38
Rheumatic Fever	0–50	14	100·6	98·3	2·3
	51–100	26	101·1	98·5	2·6
	100+	10	101·7	99·3	2·4
	Total	50	101·1	98·6	2·5
					S.E. 0·78

$$C = \frac{\text{Difference between means}}{\text{Standard Error of difference between means}} = \frac{1{\cdot}1}{0{\cdot}21} = 4{\cdot}8 \qquad P = <0{\cdot}001$$

TABLE II

MEAN DAILY MAXIMUM AND MINIMUM TEMPERATURE OVER ONE WEEK

Condition	Erythrocyte Sedimentation Rate (mm./hr)	No. of Cases	Body Temperature (° F.)		
			Mean High	Mean Low	Difference
Still's Disease	0–50	10	100·8	98·5	2·3
	51–100	31	101·3	98·8	2·5
	100+	9	100·3	98·3	2·0
	Total	50	100·9	98·7	2·2
					S.E. 1·1
Rheumatic Fever	0–50	14	99·7	98·3	1·4
	51–100	26	100·4	98·8	1·6
	100+	10	101·1	99·5	1·5
	Total	50	100·3	98·8	1·5
					S.E. 0·25

$$C = \frac{0{\cdot}7}{0{\cdot}17} = 4{\cdot}1 \qquad P = <0{\cdot}001$$

the week, and the mean maximum weekly temperature are seen to be higher in cases of Still's disease than in rheumatic fever. In these febrile cases of Still's disease there appears to be little correlation between the temperature and the erythrocyte sedimentation rate. In febrile rheumatic fever, however, the temperatures are seen to be higher with an increased erythrocyte sedimentation rate, and in cases in which the erythrocyte sedimentation rate is over 100 mm./hr the temperature in rheumatic fever is higher than in Still's disease. In rheumatic fever, although the temperature is higher with an increased erythrocyte sedimentation rate, there is no increase in temperature swing, but in Still's disease the temperature swing is greater. Finally, the temperature swing in Still's disease is significantly greater than that in rheumatic fever.

Fig. 1 illustrates the temperature (maximum and minimum daily temperatures) in four cases of Still's disease (top) contrasted with four cases of rheumatic fever (bottom). On the left is the typical temperature chart, in the middle two less typical charts and on the far right the most atypical pattern encountered in each two series.

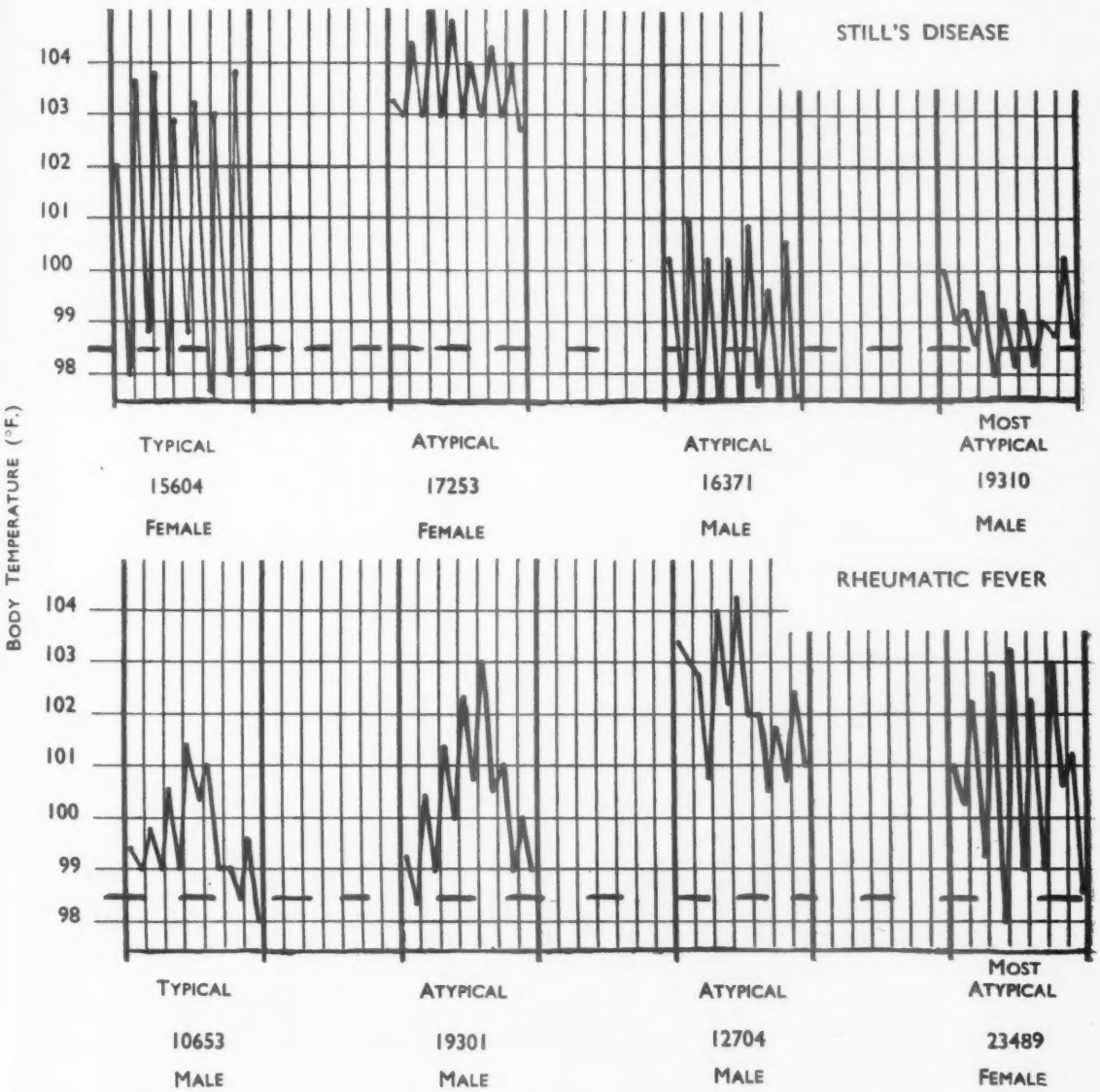

Fig. 1.—Temperature records for weekly periods in Still's disease (*top*) and rheumatic fever (*bottom*).

Discussion

These results bear out our impressions that, in children with fever and polyarthritis, temperature patterns showing high maximum levels and large swings are more usually due to Still's disease than to rheumatic fever. This is of diagnostic importance, and has been used to establish the diagnosis in obscure cases in which there was no other differentiating feature. (Differentiation is important for practical reasons, because of the prophylactic antibiotic drugs that can be given in cases of rheumatic fever.) However, exceptions are not infrequent. It is worth emphasizing (Fig. 2) that salicylates given in adequate dosage will abolish fever as much in Still's disease as in rheumatic fever. This measure is not, therefore, as some have continued to claim, of diagnostic help. The degree of fever suppression seems to depend upon the amount of salicylates given, since under a certain critical dosage escape occurs and fever returns. It is also worth remarking that the fever of Still's disease is quite frequently accompanied by the typical rash towards evening (Isdale and Bywaters, 1956), and this may sometimes also be seen in febrile adult patients; it is not always dependent on fever.

We have not dealt in this study with the course of fever. It should be emphasized that, in the absence of anti-pyretic treatment, fever may be prolonged in Still's disease, whereas it is usually of comparatively short duration in rheumatic fever, except in cases with cyclical attacks. That hyperpyrexia in rheumatic fever is now seldom seen (Miller, 1923) is probably due to the fact that less heroic doses of salicylates are given than in the late 19th century. Salicylates increase the basal metabolic rate and this may offset their effect on temperature regulation: it is probable that the epidemic of hyperpyrexia seen in the 19th century soon after the introduction of salicyl compounds was due to excess medication. We have seen hyperpyrexia in rheumatic fever only rarely, and then associated with high salicylate dosage, whereas in Still's disease high fevers of 105° and 106° occur not uncommonly in the absence of salicylate medication, and may lead, as in lupus erythematosus and other conditions with high fever, to loss of hair.

Summary

The fever in fifty cases of rheumatic fever is compared with that in fifty cases of Still's disease. A study of the height of temperature, the temperature swing, and the correlation with the erythrocyte sedimentation rate showed that the temperature

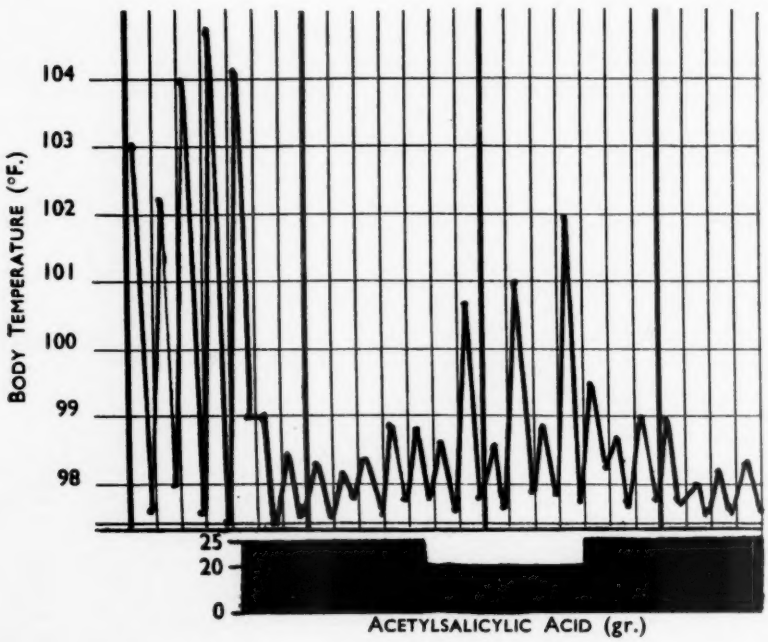

Fig. 2.—Effect of aspirin medication on the fever of Still's disease for a period of 3½ weeks. Note escape when dosage is reduced.

swing is greater in Still's disease, and that there is a direct correlation between height of temperature and erythrocyte sedimentation rate in rheumatic fever, but not in Still's disease.

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Différence entre la fièvre dans la maladie de Still et dans la maladie de Bouillaud

RÉSUMÉ

On compara la fièvre dans 50 cas de maladie de Bouillaud à celle dans 50 cas de maladie de Still. L'étude de l'élévation de la température et de ses oscillations, ainsi que sa corrélation avec la vitesse de sédimentation érythrocytaire révéla que l'oscillation pyrétique est plus prononcée dans la maladie de Still et qu'il y a un rapport direct entre la montée pyrétique et la vitesse de sédimentation érythrocytaire dans la maladie de Bouillaud, mais non pas dans la maladie de Still.

Diferencia entre la fiebre en la enfermedad de Still y en el reumatismo poliarticular agudo

SUMARIO

Se comparó la fiebre en 50 casos de reumatismo poliarticular agudo a la en 50 casos de enfermedad de Still. El estudio de la elevación de la temperatura y de sus oscilaciones, así como su correlación con la velocidad de sedimentación eritrocitaria mostró que la oscilación pirética es más pronunciada en la enfermedad de Still y que hay una correlación directa entre la subida de la temperatura y la velocidad de sedimentación eritrocitaria en el reumatismo articular agudo, pero no hay tal correlación en la enfermedad de Still.

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SALICYLATES AND THE ADRENAL CORTEX

BY

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The salicylates have been used in the symptomatic treatment of rheumatic disorders for over 50 years. They are capable of producing a striking change in the clinical picture of acute rheumatic fever and possess a smaller, but still definite, effect in rheumatoid arthritis. Their value as suppressive drugs appears to be concerned with alleviating the symptoms produced by the inflammatory processes which form a major part of the reaction of the body in rheumatic disease. The mechanism of this anti-inflammatory action of salicylates is particularly obscure. In recent years, cortisone and related hormones have also been widely used as anti-rheumatic drugs. Their clinical effects in rheumatism are very similar to those of salicylates and it has been suggested that salicylate therapy is essentially corticosteroid therapy. More sophisticated versions of this statement have included mechanisms such as stimulation of the anterior pituitary and adrenal cortex and an accelerated rate of removal of circulating corticosteroids during salicylate treatment (Hailman, 1952; Roskam, 1956; Done, Ely, and Kelley, 1958). The purpose of the present article is to show that the available evidence, if examined critically, fails to provide convincing proof of the validity of the hypothesis that the therapeutic actions of salicylates in rheumatism are mediated by the adrenal cortex or its hormones.

If salicylates act through the adrenal cortex, they may do so in one or more of three ways:

(1) They stimulate the anterior pituitary to secrete adrenocorticotrophin, which in turn causes the adrenal cortex to produce corticosteroids.

(2) They have an adrenocorticotrophic action.

(3) They may reinforce the actions of the natural hormones by increasing the tissue uptake, blocking the destruction, or by increasing tissue sensitivity to adrenal corticosteroids. They may also possess direct corticosteroid-like effects on the tissues.

There is very adequate evidence that salicylates are capable of stimulating the so-called pituitary adrenal axis in experimental animals. Thus, it has repeatedly been shown that salicylates produce depletions of the adrenal content of ascorbic acid and cholesterol (Hetzel and Hine, 1951; Van Cauwenberge, 1951; Cronheim, King, and Hyder, 1952), eosinopenia (Kelemen, Majoros, Iványi, and Kovács, 1950), and histological changes suggestive of adrenal hypersecretion (Robinson, 1951; Champy and Demay, 1951; Tronchetti and Nello, 1952). More direct evidence of pituitary and adrenal stimulation has been provided by the increased amounts of ACTH (Eades and King, 1953) and of adrenal steroids found in the plasma (Van Cauwenberge, 1954; Good, Done, Ely, and Kelley, 1957) and urine (La Barre and Hans, 1954) of animals treated with salicylates. Hypothalamic centres are also concerned because pretreatment with pentobarbital (Cronheim and Hyder, 1954) or previous destruction of the median eminence of the hypothalamus (George and Way, 1957) prevents the depletion of adrenal ascorbic acid produced by salicylates in normal animals.

However, the demonstration that salicylates cause increased adrenal cortical activity in experimental animals *via* the stimulation of hypothalamic centres and the anterior pituitary does not mean that their anti-rheumatic effects in man are produced by the same mechanism. A number of objections may be raised against this interpretation. There is no correlation between the effects of salicylate isomers on some of the experimental parameters of adrenal cortical function and their anti-rheumatic properties. Thus, both the *m*- and *p*-hydroxybenzoates, which are devoid of anti-rheumatic activity, cause significant depletions of adrenal ascorbic acid in rats (Smith, 1952a). Done, Ely, and Kelley (1956) have also reported that the meta compound causes elevated concentrations of cir

culating 17-hydroxysteroids in the guinea-pig. A further criticism is that the animal experiments have been carried out with doses of 200 to 500 mg./kg. body weight, and that these are far in excess of the usual therapeutic doses used in man. Most authors agree that there is no evidence of increased adrenal cortical activity in man following either short-term or long-term administration of therapeutic amounts of salicylate. Normal concentrations of circulating adrenal steroids, together with a normal or reduced urinary excretion of the steroids and their metabolites, have frequently been observed both in normal subjects and in patients with rheumatic fever or rheumatoid arthritis receiving salicylate therapy (Bayliss and Steinbeck, 1954; Smith, Gray, and Lunnon, 1954; Done, Ely, and Kelley, 1955; Kelley, Ely, Done, and Ainger, 1955; Peterson, Black, and Bunim, 1958). Increased plasma levels of circulating 17-hydroxysteroids have been reported to occur in children with salicylate intoxication (Done, Ely, and Kelley, 1954). This result is compatible with the animal work in that it must represent an adrenal response to stress of a toxic and non-specific nature.

The most pertinent objection to any hypothesis involving the participation of the pituitary adrenal axis in the anti-rheumatic actions of salicylates is provided by the reports that the drugs exert their anti-inflammatory effects in patients with Addison's disease (Thorn, 1958), in a rheumatoid arthritic patient whose adrenal function had been either markedly or completely suppressed (Peterson and others, 1958), and in adrenalectomized and hypophysectomized animals (Ungar, Damgaard, and Hummel, 1952). This data also serves to vitiate the suggestion that salicylates may have a direct adrenocorticotrophic action. Additional evidence against this mechanism is that hypophysectomy abolishes most of the responses suggestive of adrenal cortical stimulation, which are elicited by salicylates in normal animals (*cf.* Done and others, 1958).

There remains the possibility that salicylates may either reinforce or mimic the actions of the natural adrenal steroids on the tissues. Done and others (1958) have stated that salicylates increase the rate of removal of exogenous hydrocortisone from the circulation and suggest that this effect may mask any concomitant adrenocortical stimulation. Peterson and others (1958) have failed to confirm that therapeutic doses of salicylate increase the rate of metabolism of either hydrocortisone or corticosterone in rheumatic fever patients. No significant changes in the miscible pool or rate of synthesis of hydrocortisone were observed in their experiments. It therefore appears unlikely that salicylates reinforce the actions of the natural hormones either by inhibiting their subsequent metabolism or by increasing their uptake by the tissues. Kelemen (1956) has shown that there is no synergism between the inhibitory effects of salicylates and hydrocortisone on experimentally induced oedema in the rat, which is against the suggestion that salicylate may increase the tissue response to adrenal steroids.

If salicylates either reinforce or mimic the actions of the natural hormones then they should produce very similar, if not identical, effects on metabolism. However, important differences have been described. It has been clearly shown that therapeutic doses of salicylate cause a marked and progressive increase of oxygen consumption in normal subjects and in patients with acute rheumatic fever and subacute rheumatism (Cochran, 1952; 1954). The relief of symptoms in the rheumatic patients appeared to be associated with the maintenance of the increased oxygen uptake. Hydrocortisone does not produce similar increases in the metabolic rate (Hetzel, Williams, and Lander, 1957). Salicylates have been found to reduce the hyperglycaemia and glycosuria of patients with diabetes mellitus and of experimentally diabetic animals, whereas cortisone and other adrenal steroids produce the reverse effects (Ingle, 1950; Smith, Meade, and Bornstein, 1952; Dibenedetto dell'Aquila and Angarano, 1954; Reid, Macdougall, and Andrews, 1957). The administration of cortisone causes liver glycogen deposition in adrenalectomized animals, and hyperglycaemia and glycosuria in normal rats, but these effects are inhibited by the concurrent administration of salicylates (Smith, 1952b). The different, opposite, and even antagonistic effects of salicylates and adrenal steroids cannot be reconciled with any mechanism which assumes that the two groups of drugs have the same fundamental actions on the peripheral tissues.

Summary

The possible mechanisms by which the therapeutic effects of salicylates in rheumatism could be mediated by the adrenal cortex and its hormones are discussed. It is concluded that the administration of large amounts of salicylates to experimental animals and to man may produce a stimulation of the pituitary-adrenal axis leading to an increased secretion of adrenal steroids. However, this stimulation represents a pituitary-adrenal response to stress of a toxic and non-specific nature, and is not concerned as a mediator in the anti-inflammatory effects of therapeutic doses of salicylates. The available experimental evidence does not support the view that salicylates may either mimic or reinforce the actions of the natural

adrenal hormones on the tissues. The similar clinical effects of salicylates and adrenal steroids in rheumatic diseases must therefore be produced by different mechanisms.

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Salicylates et l'écorce surrénale

RÉSUMÉ

On considère les mécanismes possibles par lesquels l'écorce surrénale et ses hormones pourraient intervenir pour produire l'effet thérapeutique des salicylates dans le rhumatisme. On conclut que l'administration de doses fortes de salicylates aux animaux expérimentaux et à l'homme peut stimuler l'axe pituito-surrénal aboutissant à la secrétion augmentée des stéroïdes surrénaux. Toutefois, cette stimulation représente une réaction pituito-surrénale de nature toxique et non-spécifique au stress, et n'est pas en cause comme médiatrice dans les effets anti-inflammatoires des doses thérapeutiques des salicylates. Les données expérimentales existantes ne viennent pas à l'appui de la théorie que les salicylates soient capables d'imiter ou de renforcer les actions des hormones surrénales naturelles sur les tissus. Les effets cliniques similaires des salicylates et des stéroïdes surrénaux dans les maladies rhumatismales se produiraient donc par des mécanismes différents.

Salicilatos y corteza suprarrenal

SUMARIO

Se discuten los mecanismos posibles por los cuales la corteza suprarrenal y sus hormonas pudieran mediar para producir los efectos terapéuticos de los salicilatos en el reumatismo. Se concluye que la administración de dosis fuertes de salicilatos al animal experimental y al hombre puede estimular el eje pituito-suprarrenal, conduciendo a la secreción aumentada de esteroides suprarrenales. Sin embargo, esta estimulación representa una reacción pituito-suprarrenal al *stress* de naturaleza tóxica y noespecífica, sin comprometerse como mediadora en los efectos anti-inflamatorios de las dosis terapéuticas de salicilatos. Los datos experimentales existentes no vienen en apoyo de la teoría según la cual los salicilatos puedan imitar o reforzar las acciones de las hormonas suprarrenales naturales sobre los tejidos. Los efectos clínicos similares de los salicilatos y de los esteroides suprarrenales en las enfermedades reumáticas se producirían, pués, por mecanismos diferentes.

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EXPERIENCE WITH BRITISH LATEX SUSPENSION FOR AGGLUTINATION TESTS IN RHEUMATOID ARTHRITIS

BY

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Since the initial utilization of polystyrene particles by Plotz and Singer (1956) as a macroscopic indicator basis replacing sheep erythrocytes in the methods originated by Waaler (1940) and Rose, Ragan, Pearce, and Lipman (1948) for the detection of the enhancement of agglutination by a macroglobulin in sera of rheumatoid arthritic cases, many variations in practical techniques have been published. Burby and Behr (1958) recorded a method employing Bovine Cohn Fraction II gammaglobulins as the sensitizing agent. Shortly after this, a British-produced polystyrene (Latex) particle suspension became available (Coke, 1958), and a comparison of the sensitivity of this method with that of the standard Rose-Waaler or sheep cell agglutination test (S.C.A.T.) would seem to be of interest.

Ziff (1957) demonstrated that an element of normal serum protein had a capacity to inhibit agglutination, which was lost or blocked in rheumatoid arthritic serum. He claimed that his method was much more accurate so that 98 per cent. of rheumatoid patients gave positive results, but the technique involved was difficult and time consuming.

The method of Burby and Behr, used in conjunction with the original British polystyrene suspension, was also found to depend on the inhibitory capacity of normal sera and the failure of inhibitory capacity in rheumatoid arthritic sera. Modifications of the British suspension have since been made, and these require the changes in technical procedure described under "Methods".

Any numerical assessment of specific serological tests of the clinical condition in rheumatoid arthritis must rely upon the physician's definition or interpretation of the clinical condition. Until a factual aetiology for this disease process is established, the unknown variations of clinical computation must play a part in the relative value of figures derived from any series of such tests. The clinical estimation becomes more variable in the mild, early, and doubtful ambulant case than in the severe, active, hospitalized case; the latter provides intensely positive serological results which do not assist the definition of differentiation between positive and negative. The comparison, however, of two serological techniques such as the latex inhibition test of Burby and Behr, and the modified S.C.A.T. of Rose and Waaler, affords a factual numerical assessment, unaffected by clinical doubts and definitions.

While the purport of these results is the factual numerical correlation between the two technical methods, each test must be related to the clinical condition. The severity of the rheumatoid arthritis in the present series varied from the active advanced case with much functional distress to the relatively mild early case. The code of the revised criteria of the committee of the American Rheumatism Association (Ropes, 1959), together with their specified exclusions has provided the guiding principles. The clinical establishment of rheumatoid arthritis required the presence of observed joint swellings with tenderness (dissociated from any evidence of osteo-arthrosis either clinically or radiologically), measured muscle weakness, perspiration of the palms, morning stiffness, and possibly a history of cyclical variations of exacerbations and remissions. Additional evidence was given by the raised erythrocyte sedimentation rate and at times by confirmatory radiological appearances. Differentiation from the degenerative endocrine polyarthritis of the climacteric in females is a more difficult and extensive proposition, to be dealt with in a separate communication.

Methods

S.C.A.T.—The original method of Rose and others (1948) was employed with two modifications. Preliminary absorption of heterophil agglutinins (Ball, 1950) was used, and the sheep erythrocytes were sensitized by the addition of 5 minimum haemolytic doses of rabbit anti-sheep cell serum (Difco). Agglutination at a dilution of 1 : 32 or more was considered as positive.

Latex Inhibition Test.—Latex suspension was prepared by diluting the commercial preparation in glycine buffer, so that it had a transmission of 35-41 per cent. or an

optical density $E_{1\ cm.}$ = 0·46–0·39 with an Ilford filter 608, with a maximum of 690 mμ. This necessitated a dilution of 1 : 1,000 with the original Polystyrene Company's product, and of 1 : 300 with the present-day product distributed by B.D.H. All the results recorded here were made with the first original product.

0·05 ml. patient's serum is added to a very clear unscratched test tube 3 × $\frac{3}{8}$ in. containing 0·95 ml. glycine buffer. Mix and remove 0·5 ml. to a second tube containing 0·5 ml. glycine buffer, and so on to make four dilutions 1 : 20 to 1 : 160. 0·1 ml. Armour's Bovine Fraction II gamma-globulin in a strength of 0·5 per cent. in glycine buffer is added to each tube. 0·5 ml. Polystyrene suspension, diluted as above to correct transmission value, is added to each tube. The control tube contains Latex suspension and Bovine globulin only, without any added serum. All tubes are treated for 2 hours in a water bath at 56° C. The tubes are removed and allowed to stand in rack overnight at room temperature. Results are read after 18 hrs, by viewing by transmitted daylight, preferably not in sunlight. Three stages of agglutination are noted:

(*i*) A change in colour of opacity from a transparent blue tint to less transparent yellowish tint, which if undisturbed by agitation, can be seen as sedimenting with a line of demarcation below the top level of the fluid.

(*ii*) A greater degree of agglutination, with particles visible through a hand lens and some small sediment at the bottom of the tube.

(*iii*) A complete agglutination and sedimentation.

Any one of these three types occurring in the 1 : 20 and 1 : 40 dilutions is read as a positive reaction. Complete agglutination usually occurs when the S.C.A.T. reaches a titre of 1 : 256 or higher. The control tube should always show a complete agglutination.

The modern B.D.H. product does not agglutinate in the same way, but, as suggested by Burby and Behr (1959), gives a quite satisfactory reagent, if it is diluted to the correct transmission value and the Bovine gamma-globulin is increased to 0·2 ml. per tube. The same inhibitory phenomenon can then be utilized.

Glycine buffer is used as described by Burby and Behr (1958).

More recent experience suggests that these Latex colloidal suspensions may suffer with "ageing", as a result of which they become quite useless for these purposes. A control tube of Latex suspension diluted first to the correct transmission value and later as in the standard test, heated, and cooled overnight, should show a pale bluish opalescence only. If it is "aged", then opacity and agglutination may occur.

Results

Bovine Fraction II globulin by itself causes agglutination of the Latex particles. Table I shows a typical experiment and indicates the quantitative nature of the reaction. From such results, the employment of 0·1 ml. 0·5 per cent. solution of Bovine globulin as the optimal amount was derived for a standard test, being the most sensitive position giving no appreciable agglutination with normal serum to the dilution of 1 : 80. 300 consecutive specimens of sera from ambulant patients (149 with rheumatoid arthritis and 151 with other types of arthritic disease) were determined for their agglutination capacity by both tests, each of the two tests being carried out simultaneously by different sections of the laboratory staff. The results were compared after a clinical assessment of the diagnosis had been obtained. Table II (opposite) gives the general results.

The non-rheumatoid arthritic group included cases of ankylosing spondylitis, rheumatic fever, gout, osteo-arthrosis, non-articular manifestations, and physical or traumatic deformities. The definition of a polyarthritis in the female of the climacteric period and during the degenerative period in the later decades, is becoming recognized as not neces-

TABLE I

LATEX AGGLUTINATION RELATED TO BOVINE F.II AS SENSITIZING AGENT

Results with Latex Suspension (Original Polystyrene) 0·5 ml. with Different Amounts of Bovine F.II 0·5 per cent.

Dilution of Normal Serum		1/20	1/40	1/80	1/160	1/320	1/640	1/1,280
Bovine F.II 0·5 per cent. (ml. per tube)	0·2	0	0	+	++	++	++	++
	0·1	0	0	0	+	+	++	++
	0·05	0	0	0	0	+	+	++
	0·025	0	0	0	0	0	+	++

Results with Different Types of Latex Suspension (0·5 ml.) with Different Proportions of Glycine Buffer and Bovine F.II

Glycine Buffer (ml.)		0·5	0·45	0·4	0·35	0·3	0·25	0·2
Bovine F.II 0·5 per cent. (ml.)		0	0·05	0·1	0·15	0·2	0·25	0·3
Latex Suspension	Original Polystyrene	0	+	++	++	++	++	++
	B.D.H. Suspension	0	0	+	++	++	++	++

0 = No agglutination + = Partial agglutination ++ = Complete agglutination

TABLE II

SIMULTANEOUS COMPARISON OF 300 CASES WITH THE SHEEP-CELL AGGLUTINATION TEST AND THE LATEX PARTICLE INHIBITION TEST

Condition	No. of Cases	Result of Test	Test			
			S.C.A.T.		Latex	
			No.	Per cent.	No.	Per cent.
Rheumatoid Arthritis	149	+	109	73·15	105	70·5
		−	40	26·85	44	29·5
Non-rheumatoid Arthritis	151	+	4	2·7	16	10·6
		−	147	97·3	135	89·4

sarily homogeneous. This has been suggested by Olsen and Rantz (1958) and by Miall, Ball, and Kellgren (1958). Sex differences of this type were reported earlier by Ball (1952), Jacobson, Kammerer, Wolf, Epstein, and Heller (1956), and Alexander and de Forest (1954). Climacteric degenerative endocrine polyarthritis has been included as non-rheumatoid arthritis where the clinical evidence was sufficient to establish it.

Table III enumerates divergencies in greater detail; the last column shows the figure reported by Steinberg (1959) for 504 cases, in a similar comparison between the S.C.A.T. and the Plotz and Singer technique, using the Dow Latex suspension. His figures have been recalculated to the same total numbers.

Discussion

There is an apparent close relationship between the results of the two test techniques (83·3 per cent.). The correlation is closer with the Dow latex suspension although the British polystyrene latex suspension does not fall far behind. For clinical assessment the S.C.A.T. is slightly more sensitive and accurate, especially in its lower rate of false positives. The nature of this group of clinical cases provides a series of the most difficult types to differentiate both serologically as well as clinically. The latex technique allows a considerable saving in time and labour, and it is possible to get the result in a routine laboratory within 24 hours of the venepuncture. Only the established diagnosis has been taken into account, without considering the effect of treatment or the severity or duration of symptoms. The stability of positive reactions irrespective of rheumatic activity and other features has been recognized, but recent reports suggest that changes may occur as a result of treatment (Michotte, Vanslype, Tritsmans, and Verstraete, 1959; De Forest, Mucci, and Boisvert, 1958) and many of the patients in this series are in fact undergoing active therapy.

TABLE III

DETAILED COMPARISON OF CONVERGENCE AND DIVERGENCE IN SHEEP-CELL AGGLUTINATION TEST AND THE LATEX PARTICLE INHIBITION TEST

Condition	No. of Cases	Results of Tests		Present Series		Steinberg	
		S.C.A.T.	Latex	Convergence	Divergence	Convergence	Divergence
Rheumatoid Arthritis	149	+	+	92		88	
		+	−		17		9
		−	+		13		6
		−	−	27		47	
Total				119	30	135	15
Non-rheumatoid Arthritis	151	+	+	0		2	
		+	−		4		3
		−	+		16		4
		−	−	131		142	
Total				131	20	144	7
Grand Totals			No.	250	50	279	22
			Per cent. ..	83·3	16·7	92·7	7·3

It must be emphasized that these results, in so far as the latex technique is concerned, are derived entirely from the application of the Burby and Behr technique which, with the original British preparation, was found to involve the inhibition by normal sera, and they are not necessarily applicable to other techniques. Greenbury (1958) reported that, in his experience, this form of Latex suspension was inferior to the American (Dow) preparation, but his observations related to the Plotz and Singer technique, which is probably fundamentally different in its chemical reactions and does not necessarily depend upon the inhibitory functions of the normal serum. Burby and Behr (1959) report satisfactory correlative findings. The employment of these relatively simple mixtures affords a means of determining the nature of these reactions in greater detail, and it is hoped to report upon them in the near future.

Summary

Technical details of a method utilizing British Polystyrene Latex particles in the agglutination test for rheumatoid arthritis described by Burby and Behr (1958, 1959) are set out. The results of this test are compared with those of the standard sheep cell agglutination test in 300 simultaneous examinations. The two tests agreed in 83·3 per cent. of results. In assessment with the clinical diagnosis, the sheep cell agglutination test was found to be more sensitive and accurate, mainly because of the smaller number of false positive reactions.

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Essai de la suspension britannique de Latex pour les réactions d'agglutination dans l'arthrite rhumatismale

Résumé

On présente les détails techniques d'un procédé employant des particules de Latex, un polystyrène britannique, dans la réaction d'agglutination pour l'arthrite rhumatismale, selon Burby et Behr (1958, 1959). On compare les résultats de cette réaction à ceux obtenus avec la réaction d'agglutination de globules de mouton standard en 300 examens simultanés.

Il y eut un accord entre les deux réaction dans 83,3% des résultats. Par rapport aux procédés chimiques, la réaction d'agglutination de globules de mouton s'avéra plus sensible et plus précise, surtout en raison d'un nombre plus petit de réactions positives fausses.

Experiencia con suspensión británica de Latex para reacciones de aglutinación en la artritis reumatoide

Sumario

Se presentan los detalles técnicos de un método usando partículas de Latex, un polistireno británico, en la reacción de aglutinación para la artritis reumatoide, según Burby y Behr (1958, 1959). Se comparan los resultados de esta reacción a los obtenidos con la reacción de aglutinación de eritrocitos de carnero standard en 300 investigaciones simultáneas.

Ambas reacciones se acordaron en un 83% de los resultados. En comparación con los métodos químicos, la reacción de aglutinación de eritrocitos de cordero se mostró más sensible y más precisa, particularmente por dar menos falsas reacciones positivas.

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EVALUATION OF AN EPIDEMIOLOGICAL METHOD
RHEUMATOID ARTHRITIS IN LIBERIA

BY

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All current studies of rheumatoid arthritis are hindered by the lack of a precise definition of the disease. Patients in an arthritis clinic are selected, so that those with mild or short-lived forms of the disease are probably rarely seen. Because of this, better definition of rheumatoid arthritis is being sought through epidemiological studies.

Four approaches are available, either separately or in combination with one another. These include finding the prevalence rates of various factors in various populations:

(1) History of arthritis, morning stiffness, or joint swelling (Kellgren, Lawrence, and Aitken-Swan, 1953; Rubin, Rosenbaum, and Cobb, 1956);
(2) Polyarthritis demonstrated by physical examination;
(3) Radiological evidence for rheumatoid arthritis;
(4) High agglutination titres, as, for instance, with the latex-fixation test (Singer and Plotz, 1956), indicating the presence in the sera of so-called "rheumatoid factor".

Two excellent studies (Kellgren and Lawrence, 1956; Miall, Ball, and Kellgren, 1958) incorporating these four approaches emphasize the need for precise diagnostic definition for the study of comparative prevalence rates of rheumatoid arthritis in different populations, but since it is cumbersome and expensive to use all four methods, it has been suggested (Kellgren, 1958) that a serological test for rheumatoid factor alone be used to screen a population sample for rheumatoid arthritis.

Positive results of tests for the rheumatoid factor have been obtained in conditions other than rheumatoid arthritis, such as lupus erythematosus, periarteritis nodosa, and infectious hepatitis (Ziff, 1957), syphilis (Peltier and Christian, 1959), and sarcoidosis (Kunkel, Simon, and Fudenberg, 1958). Yet the study of Feldman, Mou, and Wadsworth (1958) revealed only a 0·25 per cent. incidence of positive results in what was considered a "normal" population. Kellgren and Lawrence (1956), in a study of a population sample in an industrial town in England, found 5 per cent. of men and 6 per cent. of women had positive sheep cell agglutination tests. A disturbing finding was the number of subjects with positive agglutination tests, in whom no evidence of rheumatoid arthritis was found on clinical examination. Miall, Ball, and Kellgren (1958), in a comparative study of urban and rural population samples in Wales found rheumatoid agglutination tests positive in less than 1 per cent.

Studies such as those of Feldman, Mou, and Wadsworth (1958), Kellgren, Lawrence, and Aitken-Swan (1953), Kellgren and Lawrence (1956), and Miall, Ball, and Kellgren (1958) have led to the assumption that positive serological tests for rheumatoid arthritis should be unusual in any general population. Our plan is to test this assumption through comparison of clinical and serological data in a given population said to be devoid of rheumatoid arthritis.

Methods

The Firestone Plantations Company at Harbel, Liberia, West Africa, employs some 25,000 adult males as rubber tappers on the plantation. The subjects selected for study represent members of the families of these tappers, who appeared at one of the medical clinics

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at some time or another for any of a multitude of complaints, or who wandered by the clinic and were invited in.

The non-response rate was zero, and 230 native Liberians were examined. The sample is fairly well divided between males (121, 52·6 per cent.) and females (109, 47·4 per cent.), and among the various age groups represented (Table I). The Liberian native does not keep track of his years and his actual age is anybody's guess. With the help of Liberian nurses, likely ages were chosen and the subjects were placed in 10-year groupings.

TABLE I

RESULTS OF F II TESTS IN 230 LIBERIANS

Age Group (yrs)		Male		Female		Total	
		No.	F II +	No.	F II +	No.	F II +
0-9		0	—	0	—	0	—
10-19		0	—	2	0	2	0
20-29		13	2	10	0	23	2
30-39		39	3	38	5	77	8
40-49		32	4	30	3	62	7
50-59		22	3	19	2	41	5
60 +		15	3	10	3	25	6
Total	No.	121	15	109	13	230	28
	Per cent.		12·4		11·9		12·2

Attempts were made to obtain the information set out in Table II. Such questions as stiffness on arising play a vital role in some studies of the incidence of rheumatoid arthritis (Cobb, Warren, Merchant, and Thompson, 1957; King and Cobb, 1958). However, information on stiffness and on other diseases was unreliable, for reasons of communication. Of the sixteen or seventeen tribes represented on the plantation, each has its own language, and the natives often cannot understand each other, much less us.

TABLE II

EXAMINATION

(1) Stiffness in morning or after inactivity?		
(2) Wrists	(*a*) Swelling	
	(*b*) Motion	Normal Partial ankylosis Complete ankylosis
(3) Other manifestations—Involvement of M-P or P-I-P joints, Ulnar deviation, Subcutaneous nodules		
(4) History of yaws, syphilis, etc.		

Clinical examinations were made as outlined in Table II (2 and 3). Since the incidence of wrist involvement is high in an arthritis clinic population, the wrists of each subject were examined for swelling and impairment of motion. Other manifestations of rheumatoid arthritis sought included involvement of the metacarpo-phalangeal and proximal interphalangeal joints, ulnar deviation, and subcutaneous nodules.

Serum samples from all the subjects were shipped in ice by air to the laboratories of the Edward Daniels Faulkner Arthritis Clinic of the Columbia-Presbyterian Medical Center, New York, where they were studied by the technique of the F II tanned sheep cell agglutination (Jacobson, Kammerer, Wolf, Epstein, and Heller, 1956). The differential sheep cell test (Rose, Ragan, Pearce, and Lipman, 1948) was performed on most of the positive F II sera. Yaws is clinically prevalent on the plantation, and "V.D. Reference Laboratory" (VDRL) tests for syphilis were also done on all sera. Twenty selected serum samples were subjected to paper electrophoresis.

Results

Clinical.—In the 230 subjects there was no wrist swelling. Motion was normal in 228 of 230 subjects (99·1 per cent.). None had complete ankylosis of either wrist, but two showed a partial ankylosis, one unilateral and the other bilateral. Neither of these subjects, however, showed any other clinical indications of rheumatoid arthritis. None of the 230 subjects revealed *any* of the other manifestations sought: namely, involvement of metacarpophalangeal or proximal interphalangeal joints, ulnar deviation, or subcutaneous nodules.

The clinical inquiry was extended to other areas of Liberia. Various physicians were contacted at the Firestone plantations at Harbel and Cape Palmas; Monrovia, the capital; Bomi Hills, which has two hospitals maintained by United States concerns; and the mission hospitals at Ghanta and Zor-Zor. All the physicians interviewed agreed that they had never seen a case of what they would call rheumatoid arthritis in a native Liberian.

Serological.—F II agglutination tests were positive in 28 (12·2 per cent.) of 230 serum samples (Table I). The positive results were about equally divided between males (15, 12·4 per cent.) and females (13, 11·9 per cent.). The percentage positive increased somewhat with increasing estimated age group. Titres ranged from 112 to one that was greater than 56,000 in a male in the 40 to 49 age group. Seven of the 28 positive titres were greater than 3,000.

Differential sheep cell agglutination tests were done on fifteen of the 28 F II positive sera. Only one was positive, in a male judged to be 75 to 80 years of age. His F II titre was 896. D.S.C. tests failed on two additional F II positive serum samples because of the persistence of heterophil antibody after two adsorptions with sheep red blood cells.

48 of the 230 sera (20 per cent.) had positive VDRL tests, another 20 per cent. were weakly positive or equivocal, and the remainder were

negative (Table III). Nineteen of the 28 positive F II tests were in negative or equivocally positive VDRL sera. The sample with F II titre of more than 56,000 and that with positive F II and positive D.S.C. are both among the negative VDRL sera.

TABLE III

RESULTS OF VENEREAL DISEASE REFERENCE LABORATORY TESTS

Result		No.	Per cent.
VDRL	+	48	20·9
	Weakly positive	50	21·7
	−	132	57·4
Total		230	100·0
F II +	with VDRL +	9	32·1
	with VDRL −	19	67·9
Total F II + ..		28	100·0

Of the two subjects who were found on clinical examination to have partial wrist ankylosis, the one with unilateral impairment had negative F II and negative VDRL tests, while the one with bilateral involvement had a positive F II test (titre 224) and a positive VDRL test (titre 4).

Paper electrophoresis was done on ten high-titred F II positive serum samples and ten F II negative samples. Both groups revealed varying amounts of globulin increase especially in the beta and gamma fractions. The findings were heterogeneous and non-specific.

Discussion

A significant number of positive serologic reactions (F II test) for rheumatoid factor were found in a population which is virtually devoid of clinical rheumatoid arthritis. Yet only one positive sheep cell agglutination test was found in fifteen F II positive sera. In rheumatoid arthritis, there is generally a good correlation between F II and sheep cell tests. Kunkel and others (1958) found similar test discrepancies in the sera of patients with sarcoidosis. The difference in results with the two test systems is as yet unclear. The F II test seems to be less specific for rheumatoid factor than the sheep cell test, but whether or not it is more sensitive remains to be seen.

Peltier and Christian (1959) found 11 per cent. positive F II tests in syphilitic sera, again with negative sheep cell tests. One-third of the positive F II sera in our study also had positive VDRL tests, and yaws has a high clinical incidence in Liberia, but, since the specificity of the VDRL test for syphilis in this population is unknown, no assumption can be made as to either the prevalence of yaws itself or the incidence of positive serologic reactions for rheumatoid factor in true yaws sera.

Positive F II sera were about equally divided between males and females in almost all age groups. This is in contradistinction to positive results in the sarcoid patients of Kunkel and others, where females predominated.

The problem of specificity of the various tests for the rheumatoid factor has raised many questions concerning definitions of rheumatoid arthritis which rely on serological testing. At any rate, the F II test has shown itself to be a poor screening method in the epidemiology of rheumatoid arthritis.

Summary

(1) 28 (12·2 per cent.) of 230 serum samples from native Liberians showed positive results to F II tanned sheep cell agglutination tests. Positive serologic reactions were almost equally divided between males and females. Differential sheep cell agglutination tests were done on fifteen of the F II positive sera, and in all but one the results were negative.

(2) The population sample was devoid of clinical rheumatoid arthritis. Information on previous medical history was unreliable because of language difficulties.

(3) Nine of the 28 positive F II tests were associated with positive VDRL tests.

(4) The F II tanned sheep cell agglutination test appears inadequate in screening for rheumatoid arthritis.

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Evaluation d'une méthode épidémiologique pour l'arthrite rhumatismale en Libéria

RÉSUMÉ

(1) Sur 230 échantillons de sérums des indigènes Libériens, 28 (12,2%) donnèrent une réaction positive d'agglutination des globules rouges tannés F II de mouton. Le nombre des réactions sérologiques positives fut presque le même chez les hommes et chez les femmes. On procéda à des réactions d'agglutination différentielle des globules rouges de mouton sur 15 sérums F II positifs, et le résultat ne fut positif que dans un seul cas.

(2) Il n'y eut pas d'arthrite rhumatismale clinique parmi la population de l'échantillon étudié. Des renseignements concernant les antécédants médicaux furent sans valeur, en raison des difficultés de langue.

(3) Sur les 28 réactions F II positives, neuf furent associées à des réactions de VDRL positives.

(4) La réaction d'agglutination des globules rouges tannés F II de mouton est insuffisante pour déceler l'arthrite rhumatismale.

Valoración de un método epidemiológico para la artritis reumatoide en Liberia

SUMARIO

(1) Sobre 230 muestras de sueros de indígenas liberianos, 28 (12,2%) dieron una reacción positiva de aglutinación de eritrocitos curtidos F II de oveja. Las reacciones serológicas positivas se repartieron casi igualmente entre hombres y mujeres. Se efectuaron reacciones de aglutinación diferencial de eritrocitos de oveja con 15 sueros F II positivos, obteniéndose tan sólo un resultado positivo.

(2) No hubo casos de artritis reumatoide clínica en la muestra de la población estudiada. Datos recogidos sobre los antecedentes médicos fueron sin valor en vista de dificultades de idioma.

(3) Sobre las 28 reacciones F II positivas, nueve fueron asociadas a reacciones de VDRL positivas.

(4) La reacción de aglutinación de eritrocitos curtidos F II de oveja no es adecuada para descubrir la artritis reumatoide.

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ANTI-INFLAMMATORY EFFECT OF OBSTRUCTIVE JAUNDICE IN RATS*

BY

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Detailed clinical observations by Hench (1933, 1934) established that hepatogenous jaundice ameliorated rheumatoid arthritis and fibrositis. Reports followed of remissions attending jaundice induced by the injection of bile salts and bilirubin (Thompson and Wyatt, 1938), by inoculation with infectious jaundice (Gardner, Stewart, and MacCallum, 1945), and by lactophenin (Hanssen, 1942), in addition to the many remissions attributed to cinchophen toxic hepatitis. In rats also, jaundice caused by the ligation of the bile duct inhibited an experimental arthritis produced by the injection of formalin (Selye, 1950) or of pleuropneumonia-like organisms (Snow and Hines, 1941). Selye's interpretation of jaundice and arthritis in terms of stress and inflammatory processes suggested that the anti-inflammatory effect of jaundice might be mediated by a hypersecretion of adrenal glucocorticoids (Selye, 1950). Subsequently, Selye (1954) provided evidence that an increased secretion of glucocorticoids is not prerequisite to a reduction of inflammatory processes during jaundice. He found that jaundice enhanced the anti-inflammatory effect of cortisone in adrenalectomized rats, and interpreted this as being due to a glucocorticoid-sensitizing principle in jaundice. A possibility that jaundice inhibited the inactivation of glucocorticoids was investigated by Baker (1955), and liver slices from jaundiced and non-jaundiced rats were found to inactivate equal amounts of hydrocortisone.

The present study was undertaken to obtain additional information about the role of adrenocortical hormones in inflammatory processes during obstructive jaundice. Indices of adrenocortical hormone activity and inflammatory processes were the weights, respectively, of the thymus and of the granulation tissue which formed in and about subcutaneously implanted cotton pellets. The data revealed that jaundice inhibited inflammation not only in rats with functional adrenals but also in adrenalectomized rats, and that the anti-inflammatory effect of jaundice was additive to that of cortisone.

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Materials and Methods

Experimental Animals.—Male albino rats (Holtzman Rat Co., Madison, Wisconsin) were individually caged and acclimatized to the laboratory for 2 days before the initiation of the study. At the time of cotton pellet implantation all rats were 60 days old. Rockland rat diet and tap water were provided *ad libitum*, and adrenalectomized rats were offered in addition 1 per cent. saline as drinking water.

Jaundice.—Obstructive jaundice was produced by ligating the ductus choledochus in the region of the caudate lobe of the liver. On the initial day of the experiment the rat was anaesthetized with ether, an epigastric incision was made, and the liver lobes were retracted to expose the duct. Partial obstruction of the duct was produced by tying a cotton cord around the duct and a wire (0·03 cm. in diameter) parallel to it. Then the wire was removed immediately, leaving the ligature, and the incision was closed. A sham operation consisted of all the steps in the ligation technique except that the ligature was not tied. At the end of 10 days the rats were killed and the plasma icteric index (King, 1951) was measured. Duct ligation produced a severe jaundice which corresponded to an icteric index of 24 to 32, compared with an index of 3 to 5 for sham-operated rats.

Adrenalectomy.—Bilateral adrenalectomy was performed by a lumbar approach under ether anaesthesia 72 $\pm$ 2 hrs after the duct ligation or sham operation. All adrenalectomized rats failed to show accessory adrenal tissue at autopsy.

Cotton Pellet—Granuloma Tissue Technique.—Cotton pellets weighing 6 to 8 ± 0·1 mg. were selected from those commercially supplied for use by the dental profession, and were formed into cylindrical pellets of loosely-wound fibres. At 72 ± 2 hrs after the duct ligation or sham operation, each rat was anaesthetized with ether, a short medial incision was made in the pectoral skin, and a bilateral pair of tunnels was formed in the loose subcutaneous tissue. A cotton pellet was deposited in the connective tissue at the end of each tunnel and the incision was closed with a wound clip; the average of the pellet weights was 7 mg. Two more pellets were implanted in the dorso-lateral neck regions of each rat by a similar procedure. The four pellets remained in place for 7 days, and the pellets with attendant granulation tissue were then removed, trimmed of excess connective tissue, air dried for 48 ± 2 hrs at 75° C., and weighed. The initial weight of each pellet was subtracted from the total dry weight of each granuloma. The average dry weight of tissue per granuloma was recorded for an individual rat; these values were used to calculate the mean dry weight of granuloma tissue and the standard error.

Hormonal Treatment.—This was initiated at the time of cotton pellet implantation; the compounds were injected subcutaneously in the pelvic area for 7 days.

Cortisone acetate (Merck) was administered at a dosage of 7·5 mg./kg./day. Since the microcrystals were suspended in an aqueous solution of carboxymethyl cellulose (0·5 per cent.), polyoxyethylene sorbitan monooleate (0·4 per cent.), and sodium chloride (0·9 per cent.), these ingredients, designated as Placebo-C, were injected also into rats.

Thiouracil (American Cyanamid) was injected at a dosage of 40 mg./kg./day in 0·9 per cent. saline. Thyroxine (Roche Organon Synthetic Crystals) was injected in a divided daily dose of 40 μg./kg. in alkaline solution. The placebos of these preparations were designated as Placebo-U and Placebo-X respectively.

Results and Discussion

Granuloma Tissue Formation.—The validity of the cotton pellet granuloma tissue formation method as an index of inflammatory processes has been demonstrated by Meier, Schuler, and Desaulles (1950), and the method has been used in our laboratory (Meyer, Stucki, and Aulsebrook, 1953; Stucki and Meyer, 1955). Cortisone typically inhibits granuloma tissue formation, as is shown in Table I by a comparison of non-jaundiced adrenalectomized rats which have been injected with either cortisone or the Placebo-C ($P < 0·01$).

In rats with intact adrenals, ligation of the bile duct causes a significant decrease in granuloma tissue formation when compared with the effect of the sham operation ($P < 0·01$). This is not dependent entirely upon an increased secretion of glucocorticoids by the adrenals, since jaundiced rats form less granulation tissue than non-jaundiced rats even if the rats have been adrenalectomized and main-

TABLE I

EFFECTS OF BILE DUCT LIGATION, CORTISONE ACETATE, AND THYROID TREATMENT ON GRANULOMA TISSUE FORMATION, THYMUS, AND THYROID WEIGHTS IN RATS

Treatment		No. of Rats	Granuloma* Dry Weight (mg.)	Thymus Weight (mg.)	Body Weight (g.)		Thyroid Weight (mg.)
					Initial	Final	
I Non-Adrenalectomized	Duct Ligation ..	5	8·4±0·36	125±53†	189±2·0	177±16·2	
	Sham Operation ..	5	18·4±0·48	622±28	198±2·9	262±3·0	
II Adrenalectomized	Duct Ligation + Placebo-C ..	6	11·0±0·92	491±52	186±1·6	165±5·4	
	Sham Operation + Placebo-C ..	7	14·8±0·89	659±43	183±2·8	199±6·9	
	Duct Ligation + Cortisone ..	6	6·0±0·29	43±6·4†	187±4·1	149±5·9	
	Sham Operation + Cortisone ..	6	9·2±0·31	164±82†	190±2·2	196±5·3	
	Duct Ligation + Cortisone + Thyroxin ..	6	5·9±0·78	38±3·4	193±2·6	160±6·8	7·3±0·38
	Duct Ligation + Cortisone + Placebo-X ..	4	5·1±0·70	35±3·0	189±6·1	154±6·9	6·5±0·70
	Sham Operation + Cortisone + Thiouracil ..	5	9·9±0·41	141±10	182±1·7	207±3·1	16·1±1·0
	Sham Operation + Cortisone + Placebo-U ..	4	9·9±0·82	166±17	186±3·2	198±4·6	11·4±0·5

* Mean ± Standard Error.

† Data from four rats only.

tained on weight-proportional dosages of cortisone ($P<0{\cdot}01$). Jaundice has also inhibited granuloma tissue formation when adrenalectomy, pellet implantation, and cortisone treatment have been postponed until 7 days after duct ligation or sham operation ($P<0{\cdot}01$). The mean weight ($\pm$ S.E.) of granuloma tissue obtained 7 days after such treatment is 7·9 ($\pm$0·14) mg. for four jaundiced rats, compared with 10·8 ($\pm$0·11) mg. for eight sham-operated rats.

In rats deprived of both endogenous and exogenous glucocorticoids, the granulomata formed by jaundiced rats are of a significantly lower weight than those formed by non-jaundiced rats ($P<0{\cdot}02$). The administration of cortisone further reduces granuloma tissue formation in adrenalectomized icteric rats ($P<0{\cdot}01$).

In contrast to these results, other workers have reported that adrenalectomy prevents jaundice from inhibiting granuloma tissue formation in the rat (Baker, 1955; Hershberger and Hansen, 1959). The apparent contradiction is due perhaps to their having terminated their studies 5 days or less after bile duct ligation and pellet implantation, *i.e.* sooner than in the present investigation. This explanation is consistent with their data showing that in adrenalectomized rats jaundice inhibits inflammation but to a statistically insignificant degree. Selye (1954), utilizing the granuloma pouch and topical irritation techniques, reported that obstructive jaundice potentiated the anti-inflammatory effects of cortisone. He attributed this to an increased sensitivity of jaundiced rats to anti-inflammatory corticoids. This interpretation would fail to explain the ability of jaundice to inhibit granuloma tissue formation in the absence of glucocorticoids, as shown in the present study. The data in Table II provides a basis for suggesting that the anti-inflammatory effects of cortisone and jaundice may be mutually independent and additive. Since, in Selye's study, adrenalectomized rats not receiving cortisone were maintained on deoxycorticosterone, it seems possible that the anti-inflammatory effect of jaundice was antagonized by deoxycorticosterone.

TABLE II

INHIBITORY ACTIVITY OF CORTISONE ACETATE AND/OR JAUNDICE UPON GRANULOMA TISSUE FORMATION IN ADRENALECTOMIZED RATS

Treatment	No. of Rats	Dry Granuloma Tissue (mg.)	
		Weight*	Difference in Weight from Control Group
Control (Sham Operation with Placebo-C)	7	14·8±0·89	—
Jaundice (with Placebo-C) ..	6	11·0±0·92	−3·8
Cortisone (with Sham Operation)	6	9·2±0·31	−5·6
Jaundice and Cortisone ..	6	6·0±0·29	−8·8

* mean±standard error.

Obstructive jaundice (Telkkä and Kuusisto, 1954), or cortisone (Hirvonen and Räsänen, 1954), may inhibit thyroid function in the rat. Among the possible consequences of hypothyroidism is a decreased capacity of the liver for inactivating cortisone (Yates, Urquhart, and Herbst, 1958). A postulate that hypothyroidism contributed to the anti-inflammatory effect of jaundice was therefore explored in cortisone-treated rats, by determining whether or not granuloma tissue formation was inhibited by thiouracil injections, or was increased during jaundice by thyroxin injections. The data show that administration of thyroxin to jaundiced rats maintained on cortisone does not alter the formation of granulation tissue ($P>0{\cdot}4$). Likewise, thiouracil treatment does not influence granuloma tissue formation in sham-operated rats maintained on cortisone ($P=0{\cdot}5$). The effectiveness of thiouracil is reflected in a significant increase in thyroid weights ($P<0{\cdot}01$). Thyroid weights of rats which have been injected with thyroxin and placebo-X are statistically equivalent ($P>0{\cdot}4$); no data are available to estimate the extent to which exogenous thyroxin provided adequate therapy. The results indicate that a possible difference between jaundiced and non-jaundiced rats in availability of thyroid hormone is not responsible for the observed difference in granuloma tissue formation. The failure of thyroid treatment to modify the amount of granuloma tissue may be due to the absence of adrenal tissue in these rats. The data do not preclude interactions of thyroid and adrenal glands. Selye, Sylvester, Hall, and Leblond (1944) reported that thyroidectomy facilitated the production of joint lesions in DCA-treated rats; their results were substantiated by Harrison and Barnett (1953), who correlated the arthritis with a hypofunction of the adrenal zona fasciculata caused by the thyroparathyroidectomy.

The present study does not determine whether the effects of bile duct ligation on connective tissue formation may result from direct effects of biliary products, from effects of their exclusion from the intestine, or from changes in hepatic metabolism. Since cholesterol, like cortisone, is capable of inhibiting fibroblast proliferation *in vitro* (Holden and Adams, 1957), increased blood levels of cholesterol and structurally similar bile acids may have contributed to the anti-inflammatory effect of jaundice. An impairment of food intake or efficiency of utilization in jaundiced rats (Baker, 1955)

might be conducive to the associated inhibitions of body weight and granuloma tissue formation.

Thymus.—Bile duct ligation causes involution of the thymus in rats with intact adrenals ($P < 0{\cdot}01$), but not in adrenalectomized rats injected with cortisone ($P > 0{\cdot}2$). This failure of jaundice significantly to reduce thymus weight in cortisone-treated rats may be due to the severe involution caused by cortisone. A comparison between the thymus weights of placebo-C treated jaundiced and non-jaundiced rats, in which the suspected masking effect of cortisone is absent, indicates that duct ligation alone produces thymic involution ($P < 0{\cdot}02$). Although part of the involution associated with duct ligation may be residual from the interval before adrenalectomy, the thymus weight may also be modified by factors other than adrenal hormones. Dietary vitamin B_{12} can influence the thymolytic effects of cortisone (Meites, 1951, 1952), and adrenalectomy may fail to prevent thymic involution if thyroidectomy has also been performed (Marine, Manley, and Baumann, 1924). While there is reason to suspect a hypothyroidism in jaundiced rats treated with cortisone, thyroid function does not appear to be implicated in the thymic involution occurring in these cortisone-treated rats, since thiouracil does not accelerate, nor does thyroxin impede the thymolysis ($P > 0{\cdot}3$). Although the factors responsible for thymic involution in jaundiced adrenalectomized rats are not clear, the results are consistent with the glucocorticomimetic effect of jaundice on granuloma tissue formation.

Summary

Obstructive jaundice in the rat inhibits the amount of granulation tissue which is induced by subcutaneously implanted cotton pellets. Although in adrenalectomized rats cortisone augments this anti-inflammatory effect of jaundice, this effect of jaundice persists in the absence of adrenocortical hormones. In adrenalectomized rats the inhibitory effects of cortisone and jaundice on the formation of granulation tissue appear to be mutually independent and additive. The ability of jaundice to inhibit inflammatory processes in adrenalectomized rats treated with cortisone is not dependent upon a postulated hypothyroidism.

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Effets anti-inflammatoires de l'ictère par occlusion chez le rat

RÉSUMÉ

L'ictère par occlusion chez le rat inhibe la granulation d'un tissu irrité par une implantation sous-cutanée de boulettes de coton. Bien que chez des rats privés de leurs surrénales la cortisone renforce cet effet anti-inflammatoire de l'ictère, celui-ci continue à s'exercer en l'absence des hormones surrénocorticales. Chez des rats privés de leur surrénales, les effets inhibiteurs de la cortisone et de l'ictère semblent être indépendants l'un de l'autre et additifs. Le pouvoir anti-inflammatoire de l'ictère chez des rats surrénalectomisés et traités par la cortisone ne dépend pas d'un hypothyroïdisme postulé.

Efectos anti-inflamatorios de la ictericia obstructiva en la rata

SUMARIO

La ictericia obstructiva en la rata inhibe la granulación de un tejido irritado por una implantación subcutánea de pelotillas de algodón. Aunque en ratas suprarrenalectomizadas la cortisona hace aumentar el efecto antiflogístico de la ictericia, éste persiste en la ausencia de las hormonas suprerrenales. En las ratas suprarrenalectomizadas, los efectos inhibidores de la cortisona y de la ictericia parecen aditivos e independientes el uno del otro. El poder antiflogístico de la ictericia en las ratas suprarrenalectomizadas y tratadas por la cortisona no depende de un hipotiroidismo postulado.

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URINARY INDOLES AND OTHER "EHRLICH'S REAGENT REACTORS" IN RHEUMATOID ARTHRITIS

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Recent investigations suggest that certain tryptophan metabolites such as serotonin or 5-hydroxytryptamine (5-HT) or derangements in tryptophan metabolism may be related to diseases of the connective tissue. Three of four patients with malignant carcinoid reported by Sjoerdsma, Weissbach, and Udenfriend (1956) also had rheumatoid arthritis. An association of functioning carcinoid syndrome with scleroderma has also been observed (Zarafonetis, Lorber, and Hanson, 1958).

One possible link between diseases of the connective tissue and 5-HT is the action of the latter on fibroblasts as in malignant carcinoid, where fibroblastic proliferation of the subendocardium and valves of the right side of the heart are sometimes found (Mattingly and Sjoerdsma, 1956; McKusick, 1956; Bean and Funk, 1957; Thorson, 1958). In the case reported by Bean and Funk, intense fibrosis also developed in post-operative abdominal adhesions. It appears that 5-HT may stimulate fibroblasts to form collagen. It has been suggested by Zarafonetis (1959) that the fibrotic changes in scleroderma and other related conditions result from a deranged interaction of 5-HT-mono-amine oxidase mechanisms at the tissue level.

The 5-HT content of thrombocytes has been found to be slightly lower in patients with rheumatoid arthritis than in control patients (Kerby and Taylor, 1959). Rheumatoid arthritics also show an exaggerated reactivity to 5-HT, which can be neutralized by 5-HT antagonists (Scherbel and Harrison, 1959). Preliminary observations on the uptake of radioactive 5-HT in rheumatoid arthritics suggest that the uptake increases when active disease is present, and decreases as the arthritis improves. If a potent 5-HT antagonist (1-methyl-methergine tartrate) is injected into an inflamed joint, the pain is reduced significantly, in most instances within a few minutes. Joint swelling and inflammation subside temporarily but usually not completely (Scherbel, 1959).

Clinical and experimental evidence that defective tryptophan metabolism may be concerned in scleroderma was presented by Price, Brown, Rukavina, Mendelson, and Johnson (1957), who demonstrated a large urinary output of tryptophan intermediate metabolites (especially kynurenine, 3-hydroxykynurenine, and kynurenic acid) in three cases of scleroderma after the ingestion of 2 g. tryptophan. Pyridoxine and/or Na_2EDTA administration brought the metabolism back to normal.

The present investigation is concerned with urinary indoles and other "Ehrlich's reagent reactors" in rheumatoid arthritis.

Material and Methods

25 cases of rheumatoid arthritis were studied which met the criteria of the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jessar, 1957), and 34 healthy persons from the hospital staff acted as controls.

Urinary indoles were studied by using two paper chromatographic methods:

(1) *According to Jepson* (1955).—The urine sample is applied to the paper without preliminary purification.

(2) *According to Hanson and Serin* (1955).—The urine sample undergoes purification before it is applied to the paper.

The chromatography is carried out first in alkali and secondly in acid. Ehrlich's reagent was used for the detection of spots. The sensitivity of the reaction is 0·3 μg. 5-hydroxyindole acetic acid (5-HIAA) or 1 μg. indolyl acetic acid (IAA). The following standards were used: urea, tryptophan, 5-hydroxytryptamine, 5-hydroxyindole acetic acid, indolyl acetic acid, indolyl butylic acid, tryptamine, indole, skatole, kynurenic acid, anthranilic acid, 3-hydroxyanthranilic acid, kynurenine, xanthurenic acid, nicotinic acid.

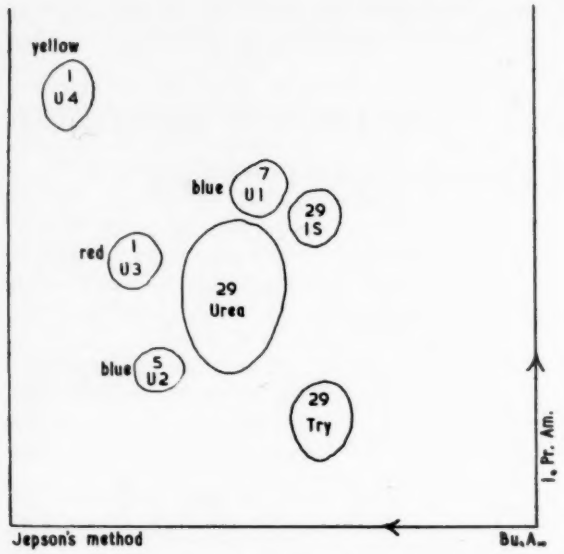

Fig. 1.—Chart of normal spots in 29 chromatograms made by Jepson's method.

Bu. A. = Butanol-acetic acid (*n*-butanol 120 ml. + water 50 ml. + glacial acetic acid 30 ml.).

I. Pr. Am. = Isopropanol-ammonia (isopropanol 200 ml. + water 20 ml. + ammonia 10 ml. (sp. gr. 0·880)).

The numerals in each ring indicate the number of cases in which each type of spot was observed.

U 1 Probably N-methylhydroxytryptamine
U 2 Probably same as Jepson's spot U 2
U 3 Probably acetyltryptophan
U 4 Probably anthranilic acid derivative

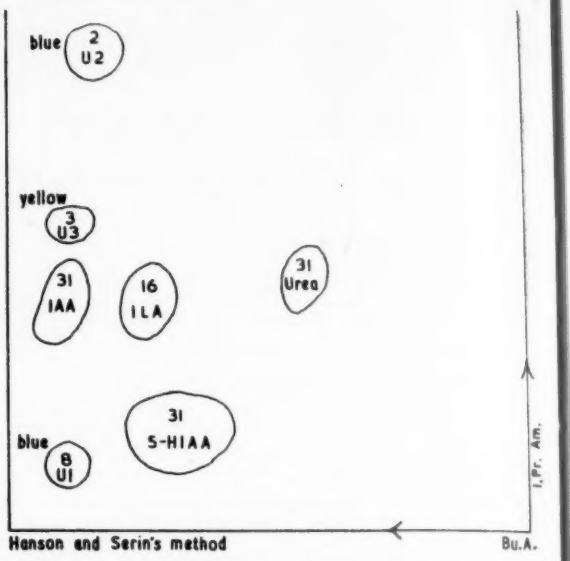

Fig. 2.—Chart of normal spots in 31 chromatograms made by Hanson and Serin's method. The numerals in each ring indicate the number of cases in which each type of spot was observed.

U 1 and U 2 = Unidentified
U 3 = Probably an anthranilic acid derivative

Quantitative determinations of 5-hydroxyindoles in morning urine were made by the method of Hanson and Serin.

Paper chromatographic studies of morning urine without supplementary L-tryptophan were carried out in twenty rheumatoid arthritics and 31 healthy controls. Urinary indole output before and after the ingestion of a loading dose of L-tryptophan was measured in five rheumatoid arthritics and three controls; 2 g. L-tryptophan was administered orally in a single dose at 8 a.m., and 24-hr urine collections were started one day before the L-tryptophan ingestion and were continued for three days.

Results

(1) Studies without Supplementary L-Tryptophan

Controls

(*i*) *Jepson's Method.*—Chromatography was performed in 29 cases. The number of spots varied from three to six (average 3·8). In addition to urea, tryptophan (Try) and indoxylsulphate (IS) were demonstrated in all cases. Indolyl acetic acid (IAA) was found in two cases. Four different unidentified spots were detected. A chart of the spots normally occurring in Jepson's system is presented in Fig. 1.

(*ii*) *Hanson and Serin's Method.*—Chromatography was performed in 31 cases. The number of spots was three to seven (average 4·1). More than five spots were found in only one case. Urea, IAA, and 5-HIAA were demonstrated in all cases. Indolyl lactic acid (ILA) was found in sixteen cases. Three different unidentified spots were detected (Fig. 2).

The paper chromatographic results were considered abnormal in rheumatoid arthritis cases only if spots other than those presented in Figs 1 and 2 could be detected.

Rheumatoid Arthritics

(*i*) *Jepson's Method.*—The spots varied in the twenty cases studied from three to seven (average 4·5). In only one case were there more than six spots.

One abnormal spot occurred in six cases, two in three cases, and three in one case. All these abnormal spots were yellow. The most characteristic localizations on the paper were "middle left" (seven cases), "up left" (four cases), and "below urea" (four cases). Yellow spots were detected in twelve cases out of twenty, but in the control series they were seen in only one case out of 29.

(*ii*) *Hanson and Serin's Method.*—The number of spots varied from two to six (average 4). It remained within normal limits in all cases.

One abnormal spot occurred in four cases and two in one case. Yellow spots were detected in

eight cases, whereas they were seen in only three out of 31 control cases. They were located either "up left" or "middle left" on the paper. Unidentified red spots were detected in two instances. 5-HIAA appeared in fourteen paper chromatograms (70 per cent.).

Some of the indole chromatograms of rheumatoid arthritics are presented in Fig. 3.

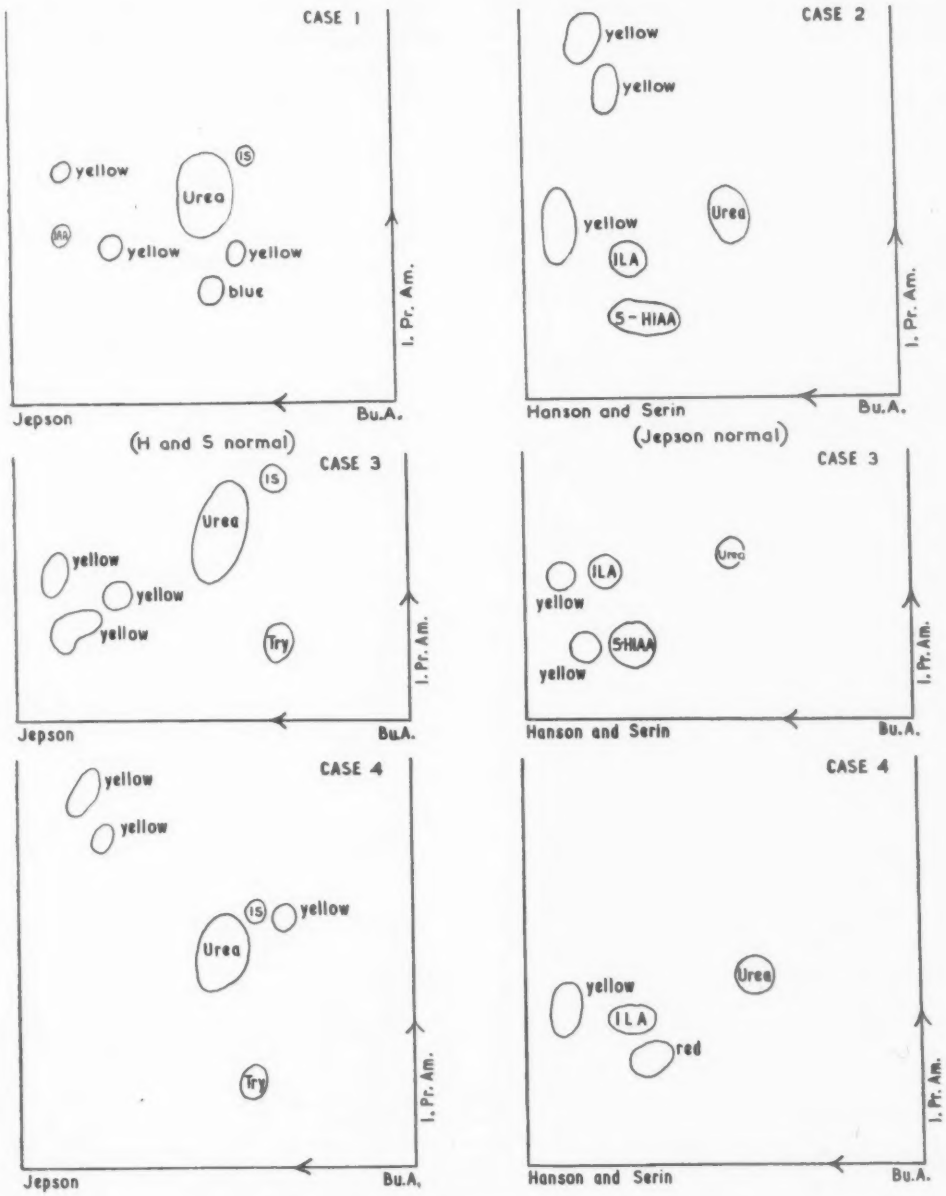

Fig. 3.—Six typical charts from cases of rheumatoid arthritis.

URINARY CONCENTRATION OF 5-HYDROXYINDOLES

Controls.—The excretion of 5-hydroxyindoles varied from 0·22 to 1·46 mg. per 100 ml. morning urine (average 0·67 mg./100 ml.).

Rheumatoid Arthritics.—The excretion varied from 0·23 to 0·78 mg./100 ml. (average 0·41 mg./100 ml.).

(2) Studies with Supplementary L-Tryptophan

The effect of the loading dose of L-tryptophan on the indole chromatograms in three controls and five rheumatoid arthritics was nil or very slight. No significant alterations in the chromatographic pattern occurred during the loading with the amino acid.

Discussion

An attempt has been made in this investigation to elucidate the intermediate metabolism of tryptophan in rheumatoid arthritis by studying the excretory pattern of urinary indoles and other "Ehrlich's reagent reactors". Taken as a whole, the indole chromatograms in the rheumatoid group deviated clearly from the control group. Unusual spots were detected in twelve cases out of twenty. In seven cases one abnormal spot occurred, which shows that the differences in individual chromatograms were generally slight.

Almost all the abnormal spots were yellow. In many of them the colour and localization resembled those of 3-hydroxyanthranilic acid and anthranilic acid, which were among the standards used. The assumption that the changes in indole chromatograms in rheumatoid arthritis were based mainly on a derangement of tryptophan metabolism *via* the kynurenine pathway seems reasonable. Tests with L-tryptophan loading did not reveal any further qualitative abnormalities.

The paper chromatographic pattern of urinary indoles in rheumatoid arthritis was not specific, since similar patterns have been observed by the authors in other systemic diseases (Oka and Leppänen, 1960).

Work is now in progress to determine the quantitative urinary excretion of certain kynurenine metabolites in rheumatoid arthritis.

Summary

The presence in the urine of indoles and other "Ehrlich's reagent reactors" was studied in twenty cases of rheumatoid arthritis and 31 healthy controls by two paper chromatographic methods and by quantitative determination. Paper chromatography before and after the ingestion of a loading dose of L-tryptophan was performed in five rheumatoid arthritics and three controls.

Slight abnormalities were observed in seven cases of rheumatoid arthritis, and more pronounced abnormalities in five other cases. The paper chromatograms showed no specific pattern. L-tryptophan loading had no effect on the indole chromatograms in the cases studied.

5-hydroxyindole acetic acid could be detected in the chromatograms of 70 per cent. of the rheumatoid arthritics and all of the control cases.

The concentration of 5-hydroxyindoles in the morning urine was slightly lower in rheumatoid arthritics than in the control cases.

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Indoles et d'autres substances sensibles au réactif d'Ehrlich dans l'urine des cas d'arthrite rhumatismale

RÉSUMÉ

On rechercha dans l'urine de 20 cas d'arthrite rhumatismale et de 31 témoins sains des indoles et d'autres substances sensibles au réactif d'Ehrlich, au moyen de deux méthodes chromatographiques sur papier et par des dosages quantitatifs. La chromatographie sur papier avant et après l'ingestion d'une dose massive de l-tryptophane fut effectuée chez 5 rhumatisants arthritiques et 3 témoins.

On observa de légères anomalies dans 7 cas d'arthrite rhumatismale et des anomalies plus prononcées dans 5 autres cas. Les chromatogrammes sur papier ne révélèrent pas d'image spécifique. L'ingestion de l-tryptophane n'eut pas d'effet sur les chromatogrammes des indoles dans les cas étudiés.

L'acide 5-hydroxyindole acétique fut décélé dans les chromatogrammes de 70% des rhumatisants et de tous les témoins.

Le taux des 5-hydroxyindoles dans l'urine matinale fut un peu plus bas chez les rhumatisants arthritiques que chez les témoins.

Indoles (C_8H_7N) y otras substancias sensibles al reactivo de Ehrlich en la orina de casos de artritis reumatoide

SUMARIO

Se estudiaron en la orina de 20 casos de artritis reumatoide y de 31 testigos sanos los índoles y otras substancias sensibles al reactivo de Ehrlich, por medio de dos métodos cromatográficos sobre papel y por determinación cuantitativa. La cromatografía sobre papel antes y después de la ingestión de una dosis de carga de l-triptófano fué efectuada en 5 casos de artritis reumatoide y en 3 testigos.

Se observaron ligeras anomalías en 7 casos de artritis reumatoide y anomalías más pronunciadas en 5 otros casos. Los cromatogramas sobre papel no revelaron imagen específica alguna. En los casos estudiados la ingestión de l-triptófano fué inefectivo sobre los cromatogramas de los indoles.

El ácido 5-hidroxi-índol acético fué encontrado en los cromatogramas del 70% de los artríticos y de todos los testigos.

La cifra de 5-hidroxi-índoles en la orina matinal fué un poquito más baja en los artríticos reumatoides que en los testigos.

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IMPORTANCE OF AN INCREASED GAMMA GLOBULIN LEVEL IN THE DETERMINATION OF Gm GROUPS IN COLLAGEN DISEASES

BY

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Since it was demonstrated that some sera of rheumatoid arthritic patients would agglutinate human Rh-positive O-erythrocytes coated with a selected incomplete anti-Rh serum (Grubb, 1956; Waller and Vaughan, 1956), this phenomenon has been extensively investigated (for example, in Finland by Julkunen, Laine, Koskinen, and Tiilikainen, 1958). Grubb and Laurell (1956) showed that this agglutination is inhibited by some human sera. The inhibitory factor has been shown to belong to the gamma globulin fraction of the serum and to be a mendelian dominantly hereditary character. The corresponding phenotype is called Gm (a+), and its frequency in normal population lies between 55 and 95 per cent. (Grubb, 1959).

65 per cent. of a sample of 477 sera from the normal Finnish population were found to be Gm (a+) (Mäkelä and Tiilikainen, 1959), the corresponding recessive character Gm (a−) being found in the remaining 35 per cent.

Present Investigations

Grubb (1959) and Podliachouk, Jacqueline, and Eyquem (1958) studied the Gm frequencies of patients suffering from various collagen diseases, and observed no significant differences in the phenotype frequencies of rheumatoid arthritis, spondylarthritis ankylopoietica (86 patients), gout (8 patients), or psoriatic arthritis (18 patients). However, a Finnish study of collagen diseases has shown a significantly different ratio of Gm groups (Tiilikainen, 1959); of 466 sera, 347 (74·5 per cent.) were Gm (a+) and 119 (25·5 per cent.) were Gm (a−).

Because of the differences between our results and those of the Swedish and French studies, we have made a clinical study of 167 patients.

Diagnosis.—128 of these patients had active rheumatoid arthritis, the diagnosis being based on the criteria of the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jessar, 1956). Of these 128 patients, thirteen (10 per cent.) had L.E. cells but no further signs of disseminated lupus erythematosus, and nine had juvenile rheumatoid arthritis. All of 25 patients with spondylarthritis ankylopoietica showed radiological changes in both the sacro-iliac joints and the spinal column, and 22 also had signs in the peripheral joints; the Bentonite flocculation test was negative in all cases. In five cases the diagnosis of disseminated lupus erythematosus could be made on the basis of articular signs, skin eruptions, presence of L.E. cells, and positive skin biopsy.

In 142 cases, a serum paper electrophoresis was done.

Method.—The Gm groups of these patients were determined by the same technique and with the same reagents as were used in the study of Gm gene frequencies in the normal Finnish population (Mäkelä and Tiilikainen, 1959). The Gm groups of some samples of normal sera were always included as controls.

Comparison was made with the normal population figures, and the differences assessed in terms of the standard error of the difference.

TABLE I

GM GROUPS IN DIFFERENT COLLAGEN DISEASES CORRELATED WITH CLINICAL SIGNS

Disease	Distribution of Gm Groups (per cent.)	No. of Cases	Duration of Disease (yrs)	Mean Erythrocyte Sedimentation Rate	Mean Percentage Gamma Globulin
Rheumatoid Arthritis	Gm(a−) 24·2 Gm(a+) 75·8	31 97	5·8 6·9	36·5 39·4	24·0 25·7
Juvenile Rheumatoid Arthritis	Gm(a−) 22·2 Gm(a+) 77·8	2 7	8·5 2·8	44·5 46·7	25·2 29·4
Spondylarthritis Ankylopoietica	Gm(a−) 28·0 Gm(a+) 72·0	7 18	6·7 10·7	61·1 37·2	
Lupus Erythematosus Disseminatus	Gm(a−) 40·0 Gm(a+) 60·0	2 3	11·0 7·3	26·0 88·3	25·3 30·9

Results

The results of Gm determinations in different types of collagen diseases are shown in Table I.

Gm (a+) tends to appear more frequently in combination with a high gamma globulin percentage in the cases of rheumatoid arthritis, and the duration of disease is longer in the Gm (a+) group.

Table II shows the correlation of the Gm group with the stage of rheumatoid arthritis (Steinbrocker, Traeger, and Batterman, 1949). No significant difference is seen between the two groups.

In Table III the correlation between the Gm groups and the gamma globulin percentage is analysed more closely; the Gm (a+) frequency tends to rise in parallel with the gamma globulin percentage.

TABLE II

GM GROUPS IN RHEUMATOID ARTHRITIS, BY STAGE OF DISEASE

Gm-Group	No. of Cases	Stage of Disease	
		I and II (per cent.)	III and IV (per cent.)
Gm(a+)	97	31	69
Gm(a−)	31	37	63

TABLE III

GM GROUPS IN RHEUMATOID ARTHRITIS CORRELATED WITH GAMMA GLOBULIN LEVELS

Percentage of Gamma Globulin	Gm(a+)		Gm(a−)		Difference ± S.E. Difference	*P*
	No. of Cases	Percentage	No. of Cases	Percentage		
Under 20	15	68·2	7	31·8		
20–25	21	65·6	11	34·4		
Total Cases with Normal Percentage	36	66·7	18	33·3	0·26	$0·7<P_1<0·8$
25–30	32	78·0	9	22·0		
30–35	13	81·3	3	18·7		
Over 35	4	100·0	0	0·0		
Total Cases with Increased Percentage	49	80·3	12	19·7	2·52	$0·01<P_2<0·02$
Normal Finnish Population	310	65·0	167	35·0		

Discussion

The Gm group has been shown to be a stable hereditary character. Other workers in Sweden and France have stated that the Gm group frequency in cases of collagen disease is similar to that seen in normal subjects. In Finland, however, a significant difference has been noted between the Gm group frequency in cases of collagen disease and that in normal subjects (Tiilikainen, 1959).

In normal sera the inhibitory potency varies with the individual. The use of selected normal sera for the calibration of the test may be inappropriate in determining the Gm groups in patients with rheumatoid arthritis. Besides the agglutination activating factor there seem to be additional constituents in the rheumatoid sera which disturb the Gm determination; this possibility is also considered by Grubb (1959).

When we look more closely at Table III, where the gamma globulin percentage in 54 patients is below 25, and when we compare their Gm frequencies (a+ 66·7 per cent.; a− 33·3 per cent.) with those of normal subjects whose gamma globulin percentage (by the same electrophoretic technique) is also below 25, we see no significant difference. But, of the 61 patients with a gamma globulin percentage over 25, 80·3 per cent. were Gm (a+) and 19·7 per cent. were Gm (a−). These findings differ significantly from those in the normal Finnish population.* Thus our results do not agree with Grubb's statement that the gamma globulin levels were not correlated with the Gm groups.

However, in Grubb's series, the cases in the Gm (a+) group included 70 per cent. with Stage I and II rheumatoid arthritis and 30 per cent. with Stage III and IV, whereas our Gm (a+) cases included 31 per cent. with Stage I and II disease and 69 per cent. with Stage III and IV. Conversely, Grubb's Gm (a−) cases included 58 per cent. with Stage I and II disease and 42 per cent. with Stage III and IV, and our Gm (a−) cases included 37 per cent. with Stage I and II and 63 per cent. with Stage III and IV. The fact that the disease was more severe in most of our patients may explain the difference in our findings.

In our 25 cases of spondylarthritis ankylopoietica, the ratio of Gm groups also showed a noticeable difference from that in the normal population, but the number of these patients is too small for the difference to be regarded as statistically significant. Of the three patients with vertebral signs alone, two had the phenotype Gm (a+).

Undoubtedly, the high gamma globulin percentage makes it difficult to determine the Gm group in cases of rheumatoid arthritis. This determination depends on the ability of a dilution of serum to inhibit the agglutination of erythrocytes sensitized with anti-Rh. This inhibitory factor is known to be present in the gamma-globulin fraction of serum. Consequently, when the gamma globulin molecules are increased quantitatively in their natural ratios, but are qualitatively "normal", it can be postulated that the molecules or molecule complexes taking part in the inhibition have also increased. It may not be necessary to infer that rheumatoid arthritis patients differ genetically from the normal population, in spite of the apparent phenotypical differences which are found in the high gamma globulin group. When the gamma globulins return to the normal level, some Gm (a+) patients may change to Gm (a−) corresponding to their true genotype. An examination of this hypothesis would exclude the possibility of genetic differences in the Gm groups of rheumatoid patients, if the investigation also extended to the patients' families and a Gm (a+) subject suffering from rheumatoid arthritis could be verified as coming from a family with Gm (a−) parents and siblings. Grubb (1959) also considered that the familial study of series of rheumatoid patients might disclose important data.

* $0{\cdot}01 < P < 0{\cdot}02$

Summary

The serum factor Gm (a+) was present in 75·8 per cent. of 128 cases of rheumatoid arthritis, in 77·8 per cent. of nine cases of juvenile rheumatoid arthritis, in 60 per cent. of five cases of disseminated lupus erythematosus, and in 72 per cent. of 25 cases of spondylarthritis ankylopoietica.

Gm (a+) appeared in 80·4 per cent. of the cases of rheumatoid arthritis with a gamma globulin percentage over 25, which is significantly greater than the frequency of 65 per cent. which has been observed in the normal Finnish population.

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Importance du taux augmenté de la gamma globuline dans la détermination des groupes Gm dans les maladies du collagéne

RÉSUMÉ

Le facteur sérique Gm (a+) fut présent dans 75,8% des 128 cas d'arthrite rhumatismale, dans 77,8% des 9 cas d'arthrite rhumatismale juvénile, dans 60% des 5 cas de lupus érythémateux disséminé et dans 72% des 25 cas de spondylarthrite ankylosante.

Le facteur Gm (a+) fut décélé dans 80,4% des cas d'arthrite rhumatismale avec un pourcentage de gamma globuline au dessus de 25; ceci représente une fréquence appréciablement plus grande que celle de 65% trouvée parmi la population finlandaise normale.

Importancia de la cifra aumentada de la gama globulina en la determinación de grupos Gm en enfermedades colágenas

SUMARIO

El factor sérico Gm (a+) fué encontrado en un 75,8% de los 128 casos de artritis reumatoide, en un 77,8% de los 9 casos de artritis reumatoide juvenil, en un 60% de los 5 casos de lupus eritematoso diseminado y en un 72% de los 25 casos de espondilartritis anquilosante.

El factor Gm (a+) fué encontrado en un 80,4% de los casos de artritis reumatoide con la cifra de gama globulina superior al 25 por ciento: esta frecuencia es significativamente mayor al 65% encontrado en la población finlandesa normal.

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COMPARATIVE STUDY OF THE HAEMAGGLUTINATION TEST AND A SIMPLE LATEX-FIXATION TEST FOR THE DETECTION OF THE RHEUMATOID FACTOR

BY

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The exact nature of the "rheumatoid factor" is unknown, but it appears to be an antibody-like substance composed of a gamma globulin complex of high molecular weight. Two groups of tests have been used to detect it: the haemagglutination test and the latex-fixation or Bentonite flocculation test. In the first group the indicator consists of sheep red cells with rabbit anti-sheep haemolysin as the reactant. In the second group the indicators are either polystyrene latex particles or bentonite particles with gamma globulin as the reactant. In both groups of tests the indicator becomes sensitized or coated with reactant which then reacts with sera containing the rheumatoid factor, causing agglutination of the indicator.

In the following series of 176 cases, serum from each case was examined for the rheumatoid factor, using a standard haemagglutination test and a simple slide latex-fixation test.

Methods

(A) Haemagglutination Test

Reagents

(1) Sheep red cells.
(2) Rabbit anti-sheep haemolytic serum.

Doubling dilutions of rabbit anti-sheep haemolytic serum were incubated at 37° C. for 1 hour with equal quantities of a 1 per cent. suspension in saline of sheep red cells. After a further hour at room temperature the agglutination end-point was read. Then a 1 per cent. solution of sheep red cells was sensitized with haemolytic serum (agglutination titre previously determined). After 30 min. equal quantities of doubling dilutions of a patient's serum (previously decomplemented at 56° C. for 30 min.) were incubated for 1 hour at 37° C. with equal quantities of the sensitized sheep cells. As a control, the patient's serum was also incubated at the same time with unsensitized sheep cells.

After a further hour at room temperature, if the agglutination titre of the sensitized cells to unsensitized cells exceeded 16, the test was considered positive.

(B) Latex-Fixation Test

Reagents

(1) Latex-globulin reagent (indicator already coated with reactant).
(2) Positive control serum.
(3) Negative control serum.
(4) Glycine-saline buffer diluent (adjusted to simplify preparation of diluted serum).

A 1 : 20 dilution of serum in glycine-saline buffer diluent was made. One drop of this was placed on a slide and to it was added one drop of latex globulin reagent. These were mixed with a stick and the slide was gently tilted from side to side for 1 min. Sera containing the rheumatoid factor produced visible flocculation of the reagent, and a smooth suspension indicated a negative reaction. Positive and negative controls were carried out. The results of the test were read as follows:

Negative	No visible flocculation as shown by negative control.
Weakly Positive (+)	Visible flocculation with small aggregates.
Strongly Positive (++)	Visible flocculation with larger aggregates and a clear background as shown by positive control.

Results

The results in the 176 persons tested are shown in Table I (opposite). The 100 cases classed as rheumatoid arthritis satisfied the accepted diagnostic criteria. The fifteen "suspected" cases were under observation as ones which might develop into rheumatoid arthritis, but it has not been possible to carry out a follow-up on this group.

Table I shows that 89 per cent. of the rheumatoid arthritis group gave positive results in the latex-fixation test, while the haemagglutination test carried out in parallel was positive in 74 per cent. Two out of fifteen "suspected" cases gave positive results in the latex-fixation test, and one in the haemagglutination test. Three out of six cases of disseminated lupus erythematosus gave positive

TABLE I

RESULTS IN 176 SERA

Test		Haemagglutination		Latex-Fixation	
Result		Positive	Negative	Positive	Negative
Diagnosis	Rheumatoid Arthritis (100)	74	26	89	11
	Suspected Rheumatoid Arthritis (15)	1	14	2	13
	Disseminated Lupus Erythematosus (6)	3	3	0	6
	Other Diseases* (45)	0	45	0	45
	Normal Controls (10)	0	10	0	10

* Osteo-arthritis (13), Gout (4), Rheumatic fever (8), Scleroderma (1), Erythema multiforme (1), Other diseases (18, including Pyelitis, Hypochromic anaemia, Pernicious anaemia, Gastric ulcer, and Bronchitis).

results in the haemagglutination test, but all the latex-fixation results were negative. It is apparent that the latex-fixation test is more sensitive and more specific for rheumatoid arthritis. No false positive results were given in this series.

Singer and Plotz (1956) described the latex-fixation test performed in tubes. This involved maintaining the constancy of the latex concentration, the make and source of the gamma globulin used, the time of incubation and temperature, and a borate buffer at pH 8·2 for optimal conditions for the test in rheumatoid arthritis. A series of tests gave the results shown in Table II.

A comparison of the latex test and the sheep cell agglutination test gave the results shown in Table III.

It may be concluded that in the present series of cases the slide latex test was superior in that it gave 89 per cent. positive results in rheumatoid arthritis as compared with the 71·3 per cent. obtained by Singer and Plotz. The probable reason for this is that the present reagents are superior to and more stable than those used by Singer and Plotz.

Bozicevich, Bunim, Freund, and Ward (1958) have described a Bentonite flocculation test for rheumatoid arthritis. The test consists of coating Bentonite particles with human gamma globulin. When mixed with the serum of patients with rheumatoid arthritis, flocculation occurs. In a series of 41 cases, 78 per cent. gave positive results. In a control series, including cases of rheumatic disease

TABLE II

LATEX TEST

Diagnosis	No. of Cases	Positive Results	
		Number	Percentage
Rheumatoid Arthritis	150	107	71·3
Osteo-arthritis and Other Arthritis	250	5	2
Rheumatic Fever and Rheumatic Heart Disease	250	4	1·6
Hyperglobulinaemia	80	4	5
Disseminated Lupus Erythematosus	20	1	5
Other Cases (Non-Articular)	560	17	3
Normal Subjects	200	2	1

TABLE III

COMPARISON OF LATEX TEST WITH SHEEP CELL AGGLUTINATION TEST

Diagnosis	Number of Cases	Latex Test (per cent. Positive)	Sheep Cell Agglutination Test (per cent.)	
			Positive	Doubtful
Rheumatoid Arthritis	150	71·3	40·7	32
Other Diseases	270	2·6	2·9	11

other than rheumatoid arthritis (Rheumatic Heart Disease, Gout, Systemic Lupus Erythematosus, Rheumatic Fever), carcinoma, and other conditions, 2 per cent. gave positive results, *i.e.* one case of systemic lupus erythematosus, one case of brain tumour with macroglobulinaemia, and one case of acute leukaemia. A series of tests on normal people all gave negative results. In the above series of cases sera tested by the sheep cell agglutination test and the Bentonite flocculation test showed agreement in 98 per cent. From these results it can be concluded that the latex test is superior to the Bentonite flocculation test in rheumatoid arthritis since only 78 per cent. were positive as compared with 89 per cent. in the present series.

Summary

176 persons (115 with rheumatoid disease and 6 with disseminated lupus erythematosus) were examined for the rheumatoid factor, using a standard haemagglutination test and a simple latex-fixation test. It is concluded that the latex-fixation test is simple and time-saving, and superior to the former test.

I should like to thank Dr. W. I. Leslie for his advice, and Dr. J. H. Glyn for his clinical help.

The reagents for the latex-fixation test were supplied by the Hyland Laboratories, California, U.S.A.

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Etude comparée de la réaction d'hémagglutination et d'une simple réaction de fixation sur latex pour déceler le facteur rhumatismal

RÉSUMÉ

On rechercha le facteur rhumatismal chez 176 personnes (dont 115 atteintes de maladie rhumatismale y 6 de lupus érythémateux disséminé) au moyen de la réaction d'hémagglutination habituelle et d'une simple réaction de fixation sur latex. On conclut que la réaction de fixation sur latex est simple, rapide et supérieure à la première reaction.

Estudio comparativo de la reacción de hemaglutinación y un simple test de fijación sobre latex para descubrir el factor reumatoide

SUMARIO

Se buscó el factor reumatoide en 176 personas (115 con artritis reumatoide y 6 con lupus eritematoso diseminado) usando la reacción de hemaglutinación clásica y un simple test de fijación sobre latex. Se concluye que el test de fijación sobre latex es sencillo, rápido y superior a la reación mencionada.

Ann. rheum. Dis. (1959), **18**, 325.

COMPARISON OF INTRA-ARTICULAR CORTISONE ANALOGUES IN OSTEO-ARTHRITIS OF THE KNEE

BY

M. J. KEHR

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The use of intra-articular steroids in the treatment of osteo-arthritis of the knee joints has not been much discussed in the literature. Burgess (1957) states that intra-articular hydrocortone is of most value in joints distended by synovial fluid. Williams (1958) found that hydrocortisone *tertiary*-butylacetate was effective over a longer period than hydrocortisone, but that both might dramatically relieve symptoms, especially pain, for anything from 2 weeks to several months. Zuckner, Machek, and Ahern (1956) compared the effects of intra-articular hydrocortisone acetate and hydrocortisone *tertiary*-butylacetate in a number of rheumatic joints, including the knee. They found no significant difference between the two compounds, but stated that 80 per cent. of joints so treated, whether rheumatoid or osteo-arthritic, responded for periods varying from 3 weeks to several months. Hollander and Moore (1956), who studied the intra-articular temperature response to injection of hydrocortisone acetate and prednisone, found that osteo-arthritic joints had a higher temperature than the normal, and that the temperature rose after intra-articular injection. Most of their patients obtained partial or complete relief for a varying period after the injections. Miller, White, and Norton (1958) injected various substances into osteo-arthritic knees, including hydrocortisone, without notable effect.

The purpose of the present investigation is two-fold:

(*i*) To compare three of these preparations;
(*ii*) To determine the value of intra-articular steroids in osteo-arthritis of the knees.

Methods

Twenty patients (ages ranging from 38 to 76 yrs) suffering from osteo-arthritis of the knees were included in the trial. In nine cases both knees were involved and in the remainder only one knee. Ten patients had some degree of swelling, and movement was much restricted in four.

The clinical diagnosis in each case was confirmed by *x*-ray examination, and rheumatoid arthritis was excluded as far as possible by estimating the erythrocyte sedimentation rate and performing the Rose-Waaler agglutination test in each case. In none was the E.S.R. higher than 12 mm./hr (Westergren), and the Rose-Waaler test was negative in each case.

Three steroids were used:

(*i*) Hydrocortisone acetate (Efcortelan—Glaxo);
(*ii*) Prednisolone *tertiary*-butylacetate (Codelcortone—Merck, Sharp and Dohme);
(*iii*) Prednisolone trimethylacetate (Ultracortenol—Ciba).

The doses given in each injection were those recommended: 25 mg. (1 c.c.) Efcortelan; 20 mg. (1 c.c.) Codelcortone; 10 mg. (1 c.c.) Ultracortenol. For the purposes of the trial only one injection of each compound was given.

Before the first injection, the degree of movement of the affected joint was roughly assessed, and the joint measured just above the patella to estimate the amount of swelling.

The patient was asked to keep a record of any improvement or otherwise in the degree of pain after the injection. Each patient was seen a week after injection. If there was no significant improvement, a different steroid from that used initially was injected, but if pain was much alleviated no further injection was given until symptoms recurred.

No controls were used, as this trial was primarily intended as a comparison between various types of steroids. The patients were not told which steroid was being administered in a particular injection, and the three compounds were adequately randomized.

No other treatment was given during the trial.

Results

The general results are shown in Table I, and a comparison between the three types of steroid is set out in Table II (opposite).

Only three patients failed to derive any benefit from the treatment, and eight obtained relief lasting a month or more. Some of these had had long courses of physiotherapy and/or analgesics before attending the clinic.

An interesting and entirely unexpected feature of the trial was the marked divergence shown by some of the patients in their response to the three types of steroid used:

Case 6, a woman aged 56, and **Case 7, a man aged 53,** obtained 6 months' freedom from pain after one injection of Codelcortone, but failed to respond to the other steroids.

Case 10, a man aged 67, obtained no relief with Codelcortone, but 4 months' complete relief with Ultracortenol.

Case 11, a woman aged 59, was free from pain for 6 months after an injection of Efcortelan, whereas the other steroids afforded her no relief at all.

Case 13, a woman aged 57, obtained 3 months' relief after the injection of Ultracortenol, but no relief from the other steroids.

The degree of swelling was affected as well as pain. Of the ten patients with swelling of the knees, eight showed a reduction ranging from 0·5 to 3 in. Of the four patients who had severe restriction of movement, two improved considerably, but the other two were unaffected.

The progress of three typical cases is shown below:

Case 11, a housewife aged 59, had had severe pain in both knees for some months, and experienced great difficulty in getting up and down stairs. On examination both knees showed moderately advanced osteo-arthritis without swelling. Analgesics and a long course of physiotherapy had had no effect. After one injection of 25 mg. Efcortelan into each knee she was completely free from pain for a period of 6 months.

Case 10, a man aged 67, who had suffered from severe pain in his left knee, unrelieved by analgesics, for 2 months, was completely free from pain after one injection of Ultracortenol and remains so 4 months later.

TABLE I

KNEE INVOLVEMENT AND RESPONSE IN 20 CASES

Case No.	Sex	Age (yrs)	Knee Involvement		Response	
			Left	Right	Relief of Pain	Swelling
1	F	76	Severe	Severe	Up to 25 days	None
2	F	73	Severe	Severe	Some in right knee	++ not reduced
3	F	54	Severe	Severe	Complete for 4 weeks	Reduced by ½ in.
4	F	38	Moderate	None	14 days	None
5	M	67	Moderate	None	None	None
6	F	56	None	Moderate	6 months at least	Reduced by 1 in.
7	M	53	Moderate	Slight	Right, no pain; Left, some improvement	None
8	F	54	Moderate	Severe	None	++ not reduced
9	F	62	Severe	None	Some relief at first; later no response	Much reduced by at least 3 in.
10	M	67	None	Moderate	Complete for 4 months	None
11	F	59	Moderate	Moderate	6 to 7 months	None
12	F	57	Severe	None	30 days	Reduced by ½ in.
13	F	57	None	Moderate	3 to 4 months	None
14	M	65	Moderate	None	None	No response
15	M	63	Moderate	None	Complete for 6 weeks	None
16	F	57	Severe	Severe	Slight	Reduced by ½ in.
17	M	63	Moderate	Nil	Improved for 14 days	Reduced by 1 in.
18	F	68	Moderate	Moderate	So far 21 days	None
19	F	53	Moderate	Moderate	Right, 14 days; Left, 21 days	Left reduced by ½ in.
20	M	59	Severe	Not painful	4 weeks	Reduced by 1 in.

Case 20, a man aged 59, had had 4 months' physiotherapy without effect for advanced osteo-arthritis of the left knee, which was swollen and very painful, and showed gross radiological changes. After one injection of 10 mg. Ultracortenol he was entirely free from pain for a period of 4 weeks and the circumference of the knee decreased by 1 in. within a week. He has been kept free from pain by injections of Ultracortenol at intervals of 4 to 6 weeks.

The three patients who did not respond were Cases 5, 8, and 14. Of these only Case 8 had severe osteo-arthritis with swelling and limitation of movement, and this patient has so far not responded to other medical treatment, including analgesics and physiotherapy. The other two patients had rather mild arthritis, but with limitation of movement in one, and both responded very well to a course of short-wave therapy to the affected knee.

Discussion

The value of intra-articular steroids in the treatment of osteo-arthritis of the knees has been convincingly demonstrated in the past years at various hospitals and clinics, but the results obtained have not always been published. The author feels that this is the treatment of choice, and superior to analgesics, physiotherapy, and the injection of other compounds into the knees.

It has been widely held that intra-articular steroids are of value only in cases of articular swelling. The results obtained in this series do not entirely support this view; three of the patients who obtained most relief had no joint swelling at any time during their attendance at the clinic.

None of the steroids used was entirely superior to the others, yet in six cases, where two of the three failed, the third proved to be singularly successful. No reason can be advanced for this finding, the active contents of the three compounds being very much alike. Nevertheless, it appears that, if one type of steroid fails, another may succeed.

Summary

Twenty patients suffering from osteo-arthritis of the knees were given intra-articular injections of

TABLE II

RESPONSE TO INTRA-ARTICULAR STEROIDS IN 20 CASES

Case No.	Response to Various Steroids		
	Efcortelan	Codelcortone	Ultracortenol
1	Right, 25 days; Left, 18 days	Right, 28 days	Left, 8 days
2	Right, 7 days; Left, none	None	None
3	None	28 days	14 days
4	14 to 21 days	14 days	Not known
5	None	None	Slight for 2 to 3 days
6	None	6 months	None
7	None	Right, full relief; Left, some relief	None
8	None	Right improved at first	None
9	28 days	7 days	15 days
10	Not used	None	4 months
11	6 months	Left, 12 days	None
12	30 days	12 days	None
13	Slight	14 days	3 months
14	None	None	None
15	6 days	6 weeks at least	Not used
16	None	Slight	None
17	14 days	14 days	Not used
18	None	None	21 days
19	None	Right, 14 days	Left, 21 days
20	Not used	Not used	4 weeks

three types of steroid. No conclusive evidence was obtained that one type of steroid was superior to the others, but it was shown that if one steroid fails to give relief, it is always worth while trying another.

It is felt that intra-articular steroids should be tried in every case of painful osteo-arthritis of the knee, whether there is swelling or not.

I wish to thank Dr. E. T. D. Fletcher, without whose advice and constant encouragement this paper could not have been written; Dr. H. Coke, pathologist, Charterhouse Rheumatism Clinic, for his valuable help; and the firms of Glaxo, Ciba, and Merck, Sharp, and Dohme who provided materials for the trial.

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Comparaison des analoguës de la cortisone par voie intra-articulaire dans l'ostéo-arthrite du genou

RÉSUMÉ

Vingt malades atteints d'ostéo-arthrite des genoux reçurent des injections intra-articulaires de trois types de stéroïde. On n'obtint pas de preuve concluante qu'un type de stéroïde soit supérieur à un autre, mais on démontra que lorsqu'un stéroïde échoue, il vaut bien en essayer un autre.

On croit que l'injection intra-articulaire d'un stéroïde doit être essayée dans tous les cas d'ostéo-arthrite douloureuse du genou, tant en présence qu'en absence d'une tuméfaction.

Comparación de análogos de la cortisona intra-articular en la ósteoartritis de la rodilla

SUMARIO

Veinte enfermos con ósteoartritis de la rodilla recibieron inyecciones intra-articulares de tres tipos de esteroides. No se obtuvo prueba conclusiva de que un tipo de esteroide sea superior a otro, pero se comprobó que al fallar uno, vale la pena ensayar un otro.

Se cree que una inyección intra-articular de un esteroide debe usarse en todos los casos de ósteoartritis dolorosa de la rodilla, con o sin hinchazón.

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BOOK REVIEW

L'Épaule, en pratique rhumatologique (The Shoulder in Rheumatological Practice). By S. de Sèze, A. Ryckewaert, and M. Maître. 1959. Pp. 167, 208 figs, bibl. Masson, Paris.

This little book summarizes the authors' experiences of shoulder lesions over a 5-year period at the Hôpital Lariboisière, Paris. The standard of the 208 illustrations (mostly radiographs) is exceptionally high and the text is supported by numerous individual case reports, and by reference to the relative frequency of the various lesions in the authors' practice.

The opening chapter deals briefly but clearly with the anatomy of the shoulder, emphasizing the two chief synovial cavities, glenohumeral joint and subdeltoid bursa, which take part in shoulder movement, and stressing the relative thinness of the barrier between them. The acromio-clavicular and sterno-clavicular joints and the subscapular gliding plane receive brief mention. Two arthrograms, using injected contrast media, illustrate a normal and an abnormal shoulder joint. One could have wished for more of these, and also for more reference to photographs and dissections of the morbid anatomy of the shoulder at operation or autopsy. The sections on gout, ankylosing spondylitis, and rheumatoid arthritis are adequate. (Many British rheumatologists would question the statement that the shoulders are far more frequently involved than the feet in rheumatoid arthritis.) The authors emphasize the need for early treatment of shoulder lesions in rheumatoid arthritis and ankylosing spondylitis in order to prevent serious disability. The section on tuberculous arthritis of the shoulder is one of the best in the book, since it emphasizes, with case reports, the insidious onset of such lesions, which may closely mimic (and be treated as) a simple peri-arthritis of the shoulder unless the diagnosis is thought of and *x* rays taken. The often neglected subject of osteo-arthrosis of the shoulder receives attention, cases of apparently primary osteo-arthrosis being cited as well as cases in which the arthrosis is secondary to previous disease, trauma, and congenital deformity. The section on the bone diseases and tumours affecting the shoulder is valuable though hardly comprehensive. The book is least convincing when it comes to the treatment of periarthritis of the shoulder. A wide variety of procedures are tendered as beneficial without the proviso that the condition frequently improves spontaneously. Nor is it clear why it should be recommended that phenylbutazone (which is rapidly effective by mouth) be given by injection or suppository; this can hardly be due to regard for the stomach, since prednisolone in a dose of 30 to 40 mg./day is suggested as an alternative. These, however, are minor criticisms. The book sets out to be a handy and practical reference book on the problems of the shoulder as seen in a rheumatology clinic, and as such it is one of the best of its kind. (It was awarded the Acqui prize for a work published in 1958.)

A. St. J. Dixon.

CANADIAN RHEUMATISM ASSOCIATION

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HEBERDEN SOCIETY

A clinical meeting was held on October 2, 1959, at the Postgraduate Medical School, Hammersmith, the President, Prof. J. H. Kellgren being in the chair.

Heberden Round.—William Heberden discoursed on clinical problems at the bedside with description, commentary, and question. The tradition of the Heberden Round is now established as affording an opportunity for clinical presentation of patients suffering from rheumatic disease. The round for 1959 was conducted by Prof. E. G. L. Bywaters, who took as his theme "The Seven Ages of Man in Rheumatoid Arthritis", and the round illustrated the incidence, symptomatology, and course of the disease from the cradle to the grave. Generous acknowledgement was given to the help received over the years from assistants and collaborators at the Hammersmith Hospital and the Canadian Red Cross Memorial Hospital, Taplow. The round was, indeed, a chimaera of the many contributions to our knowledge of the natural history of rheumatoid arthritis that have been published from these hospitals during the past 14 years.

Evidence supporting the concept of the common identity of the juvenile and adult forms of the disease was presented, and the rigidity of classifications which excluded some patients with apparent rheumatoid lesions was criticized. The existence of numerous non-articular and visceral lesions was indicated and their importance stressed. In a round livened by illustration and commentary and laced with academic wit, the final demonstration was an excursion into the neighbouring province of gerontology—a 20th-century octogenarian who had previously suffered from rheumatoid arthritis was now in complete remission, "sans arthritis" but plus every faculty.

Clinical demonstrations of "Early Radiological Features of Rheumatoid Arthritis" and "Technique of Bone Biopsy" were arranged by members of the staff of the Postgraduate Medical School, and the following papers were presented:

Fractures in Still's Disease (Drs. B. W. D. Badley and B. M. Ansell, *Taplow*).—To assess the importance of steroid therapy as a predisposing cause of fractures in Still's disease, 216 patients suffering from this condition who had been treated at the Canadian Red Cross Memorial Hospital, Taplow, and followed to the present time, were reviewed. 25 children had sustained 33 fractures and on nineteen occasions these followed a definite episode of trauma. Of these 25 children, nine were on maintenance steroid therapy in a daily dosage varying between 25 and 100 mg. cortisone or its equivalent.

A high proportion of the fractures occurred in girls in whom the disease had commenced before the age of 5 years and had been particularly severe. Five patients on maintenance steroid therapy developed crush fractures of the vertebral bodies, without any antecedent history of trauma. More than half of the 25 patients who sustained fractures had at some time had a period of complete rest in bed elsewhere for 3 months or more.

Discussion.—Dr. G. R. Fearnley (*Gloucester*) noted that vertebral collapse during steroid therapy appeared to be more common in children than in adults, and asked whether children on steroid therapy should not have routine *x* rays of the spine.

Dr. A. G. S. Hill (*Aylesbury*) thought that vertebral collapse was most common in the very young and the very old.

Prof. E. G. L. Bywaters (*London*) agreed that it was very important to keep a check on the spine, particularly in the young and the elderly, and especially in those who had been immobilized for some time.

Dr. J. H. Glyn (*London*) asked about the use of non-virilizing anabolic hormones.

Dr. Badley replied that two girls were given "Nilevar", but both had developed side-effects.

Dr. M. D. Milne (*London*) said that he had had experience of anabolic steroids only in acute renal failure. They retarded protein breakdown in women especially, so that dialysis was rarely needed. In short-term treatment of 3 or 4 weeks only he had not seen virilization, but that was not to say that it did not occur in rheumatoid patients.

Mr. J. C. F. Cregan (*Buxton*) wondered if there had been any variation from normal in the healing of the long bone fractures.

Dr. Badley thought not.

Prof. J. H. Kellgren (*Manchester*) asked about the duration of treatment and dosage. He thought that dosage for 4 or 5 years was the type which caused osteoporosis and crush fractures.

Dr. Badley replied that dosage levels had been mentioned. In one patient a crush fracture had occurred after 7 months of continuous therapy.

Pharmacological Gout (Dr. A. St. J. Dixon, Dr. J. T. Scott, and Miss D. Rix).—Several drugs were known to raise serum urate levels and to depress uric acid excretion.

Both pyrazinamide, an anti-tuberculous drug, and chlorothiazide, an oral diuretic, had been indicted in this respect and recorded as having produced acute gouty arthritis. Detailed observations on a patient who developed hyperuricaemia and acute gouty arthritis during pyrazinamide therapy were presented. It was found that the hyperuricaemic effect of pyrazinamide was more effectively suppressed by small doses of aspirin than by large doses of probenecid. The difficulty in explaining these findings by conventional theories of uric acid excretion were discussed, and the suggestion that there might be at least two sites in the nephron where urate transfer could be modified, was considered.

Discussion.—DR. C. T. DOLLERY (*London*) showed one slide, concerning sixteen patients whose serum uric acid was measured before and after treatment with antihypertensive drugs. Eight were treated with pempidine, seven with chlorothiazide, and one with mecamylamine. Before treatment only one patient had a serum uric acid higher than 6 mg./100 ml., but after treatment six patients on pempidine and five on chlorothiazide had values of 6 mg./100 ml. or higher. There were two dangers from this drug-induced hyperuricaemia: prolonged elevation of the serum uric acid might give rise to gouty arthritis in hypertensive patients under treatment, and hyperuricaemia might accelerate the deterioration of renal function in these patients.

Review of Bone Biopsies in a Rheumatology Unit (DRS. J. T. SCOTT and A. ST. J. DIXON and PROF. E. G. L. BYWATERS): Skeletal pain due to metabolic bone disease might cause a patient to be referred to a rheumatism clinic. Biopsy was a valuable investigation in the diagnosis of such bone diseases, and the techniques of iliac crest bone biopsy with the Nordin-Sacker needle under local anaesthetic, and the preparation of both decalcified and un-decalcified specimens, were described. The results of 23 biopsies performed on sixteen patients were discussed, and the value of the procedure in the diagnosis of osteomalacia was stressed. It appeared that pain was not necessarily related to the histological finding of osteomalacia; that osteomalacia might, itself, cause an elevated sedimentation rate; that osteomalacia might exist in the absence of accepted biochemical and radiological evidence, and might cause or aggravate arthritis of the weight-bearing joints.

Discussion.—PROF. J. H. KELLGREN (*Manchester*) felt that attention should be paid to the paramount importance of bone biopsy in these cases, an investigation much neglected in the past.

DR. O. SAVAGE (*London*) wondered if bone pain attributed to osteoporosis in old people could in some cases be due to osteomalacia, secondary to renal or intestinal disease. Was there any way, apart from bone biopsy, of diagnosing osteomalacia?

DR. SCOTT replied that there was considerable suspicion that bone pains in some old people were due to osteomalacia, and said they were planning to examine bone biopsies in such patients.

DR. DIXON said that, apart from bone biopsy, there was no *single* test, clinical, biochemical, or radiological, by which osteomalacia could be excluded.

A speaker raised the question of the ethical position. Was it a painful procedure and how was it justified?

DR. SCOTT replied that they did not do a biopsy without considerable preliminary thought. Osteomalacia was treatable, responding to calciferol with or without a gluten-free diet, and its diagnosis was full justification for biopsy which was a painless procedure by their technique.

PROF. J. H. KELLGREN (*Manchester*) thought that, considering the readiness with which other procedures were carried out, the case for bone biopsy was very straightforward.

Palindromic Rheumatism (DR. B. M. ANSELL and PROF. E. G. L. BYWATERS).—The concept of "palindromic rheumatism" as a separate clinical entity, characterized by multiple attacks of acute or sub-acute joint pain subsiding without residua, was examined. The authors had studied 28 patients who fulfilled these criteria and were either at the Hammersmith Hospital or at the Canadian Red Cross Memorial Hospital, Taplow, between 1948 and 1956, and reviewed them to date. Eighteen of these patients now had a definite chronic polyarthritis, with a positive D.A.T. test in thirteen, and nodules in ten. It was considered that palindromic rheumatism was merely a variant, and mode of presentation, of rheumatoid arthritis, and that the majority of such patients if followed long enough would eventually show residual signs of rheumatoid disease. That the period of follow-up must sometimes be very long was shown by one patient whose disease remained in the palindromic phase for 24 years.

Discussion.—PROF. J. H. KELLGREN (*Manchester*) noted that the Mayo Clinic had done a follow-up on Hench's original cases, and asked how the two studies compared.

DR. ANSELL said that she had not yet seen their report.

DR. A. G. S. HILL (*Aylesbury*) had studied 21 patients suffering from "palindromic rheumatism" who were followed up over a shorter period. Eleven now had erosions, and 80 per cent. had a positive D.A.T. test, almost the same frequency as in classical rheumatoid arthritis. Special features were the frequent involvement of the shoulders and a sex ratio of two men to one woman. He agreed that episodes could continue into the phase of chronic rheumatoid arthritis, still giving a history of acute, painful attacks lasting 24 to 36 hours. When the histories of patients with definite rheumatoid arthritis were reviewed, a palindromic or episodic type of onset was found in 10 to 15 per cent.

DR. R. A. SHADDICK (*Enfield*) asked about arteritic lesions.

DR. ANSELL reported that they had not been particularly impressed in respect of involvement of the shoulders. Finger contractures had been a common feature during the palindromic phase. The skin lesion illustrated was probably an arteritic lesion round the nail.

PROF. E. G. L. BYWATERS drew attention to the two phases of the disease. One was a resolvable phase and

the other appeared to perpetuate itself. The reason was not known, and that was an important field for work. The Rose-Waaler factor did not appear to have a great deal to do with it as the Rose-Waaler test had remained positive in one of his patients who had apparently completely resolved.

In closing the meeting the President thanked Professor Bywaters and his staff for their presentations, and the Dean of the Postgraduate Medical School for the hospitality which had been extended to the Society.

LIGUE EUROPÉENNE CONTRE LE RHUMATISME

IV RHEUMATOLOGICAL CONGRESS

Istanbul, September 28-30, 1959

There were over 400 medical delegates to the congress and 200 associates—including a fair number from America and Canada. Some 120 members travelled by sea from Marseilles or Genoa *via* Naples and Athens and used the ship as a floating hotel during the congress.

On the medical plane, perhaps the most important conclusion was the acceptance of Anturan (G.28 315) as the best and safest uricosuric agent for use in gout (Kersley, Ogryzlo, and others). The value of G.27 202 as a substitute for Butazolidin was reviewed; this drug is of a lower potency but of much less toxicity, and may well be a useful substitute where Butazolidin is indicated but where toxic symptoms occur or are feared (Hart, Graham, and others). Steroids were not so greatly in favour as in the past, and Dexamethasone was stated to have no advantage over the rest, except perhaps in patients with diabetes (Platz, Ballabio, and others).

Considerable concern was shown at the danger of steroids being "sold over the counter" in many countries, and at the way in which they could easily be obtained without prescription even when medical prescription was officially required (Forestier). The Russians made an interesting claim that a virus of the coxsackie group may well be a factor, in conjunction with the streptococcus, in rheumatic fever (Zalessky). De Sèze gave an interesting paper on the morbid anatomy of the frozen shoulder. A report of all papers given at the Congress will be published later. Many useful discussions took place and all participants appeared to agree that the proceedings had surpassed their expectations in the opportunities which were afforded for both learning and recreation.

Istanbul is a wonderful city of mosques and palaces, situated in spectacular scenery overlooking three stretches of water, the Golden Horn, the Bosphorus, and the Sea of Marmora. Every effort was made to display the city's beauty to the members of the congress, together with its treasures, which include what are probably the finest collections of Chinese porcelain and of well-preserved sarcophagi in the world.

The city presents a fantastic contrast of oriental splendour alongside extreme poverty, but the present government is carrying out one of the greatest reconstruction and slum clearance schemes ever contemplated, bulldozing buildings and roads in the bad areas so that the dust and rubble remind one of some of the worst scenes after the blitz. On the periphery, in contrast, are to be seen community centres designed by leading modern architects.

The meeting was a great success in every way thanks to the exertions of our Turkish hosts, whose task had been made more difficult by the death of their first Chairman, Prof. N. Ş. Dirisu, six months before. The Organizing Chairman of the Congress Committee was Prof. Z. Paykoç with Prof. Kocas as Vice-Chairman and Secretary.

Officers of the Ligue Européenne

PRESIDENT: Prof. A. Robecchi (*Italy*), taking over from Dr. J. Forestier (*France*).

VICE-PRESIDENTS: Prof. G. Edström (*Sweden*) and Prof. F. Lenoch (*Czechoslovakia*).

SECRETARY: Prof. L. Michotte (*Belgium*).

ASSISTANT SECRETARIES: Dr. G. D. Kersley (*England*) and Prof. A. Jung (*Switzerland*).

Future Arrangements

The next International Congress will be held in Rome from September 4 to 7, 1961, and the next European Congress in Sweden in July or August, 1963.

Ann. rheum. Dis. (1959), **18**, 333.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi *of steroid therapy.*

Acute Rheumatism

Group-A Beta-Hemolytic Streptococci and Rheumatic Fever in Miami, Florida: I. Bacteriologic Observations from October, 1954, to May, 1955. SASLAW, M. S., and STREITFELD, M. M. (1959). *Dis. Chest.*, **35**, 175. 3 figs, 8 refs.

As part of a study of the aetiological relationship between rheumatic fever and Group-A β-haemolytic streptococci, the prevalence of these organisms in the throats of school children in Miami, Florida, was investigated. The investigation was divided into two parts:

(1) An intensive study of 333 children aged 6 to 9 years attending three different schools—representing a low-income white, a high-income white, and a mixed-income Negro population respectively—who were examined at monthly intervals from October, 1954, to May, 1955;

(2) A concurrent survey carried out on 1,200 children of the same age group in 48 additional elementary schools throughout the same county area, one culture only being taken from each child and 150 being examined each month.

The intensive study revealed that 44·7 per cent. of a monthly average of 304·6 children examined harboured Group-A organisms at least once during the period of study. The percentage of children harbouring the organism decreased slightly with age, was higher for girls (44·4 per cent.) than for boys (38·3 per cent.), and was much higher in the Negro school (73·3 per cent.) than in the white schools (50·4 and 54·5 per cent.). Despite this last finding, however, the proportion of all cultures taken which yielded positive results was approximately the same in all three schools. Ten different typable strains of Group-A β-haemolytic streptococci were isolated; Type 6 was the most common and occurred most frequently in March, April, and May. At no time were two different types isolated during the same period, though combinations of typable and non-typable organisms were encountered 4 times.

In the wider survey the average and monthly isolation rates of Group-A organisms were similar to those in the first group, and the same variations with age and sex were noted, suggesting that the findings in these respects in the intensive study were representative of the area as a whole. But although β-haemolytic streptococci were recovered more commonly from Negroes (31 per cent.) than white children (22 per cent.), Group-A organisms were more frequent among the white (15 per cent.) than the Negro children (11·4 per cent.) in the second study.

The authors observed that although at one time the isolation rates of Group-A Type-6 organisms rose in two classes to 33 and 50 per cent. respectively, there was no noticeable alteration in the monthly absentee rate; the relationship between streptococcal isolation rates and respiratory illness is to be the subject of a further communication, as also are various serological and immunological observations and their relation to rheumatic fever and glomerulonephritis. The value of a duplicate plate technique in surveys of this kind is emphasized, cultures made on different media from pairs of swabs taken simultaneously in the present survey giving discrepant results in 40 per cent. of cases. *D. M. Weir.*

Effect of Penicillin on Acute Rheumatic Fever and Valvular Heart Disease. MORTIMER, E. A., VAISMAN B., S., VIGNAU I., A., GUASCH L., J., SCHUSTER C., A., RAKITA, L., KRAUSE, R. M., ROBERTS, R., and RAMMELKAMP, C. H. (1959). *New Engl. J. Med.*, **260**, 101. 7 figs, 22 refs.

The experiment here reported from the University of Chile and Western Reserve University, Cleveland, Ohio, was designed to show whether or not the rapid elimination of haemolytic streptococci from patients suffering from acute rheumatism would materially affect the acute course or the late results of the disease. All patients (97) admitted to three hospitals in Santiago between June and September, 1956, with symptoms of rheumatic fever were included in the study. They were divided into two main groups, one comprising patients experiencing a first attack and one comprising those suffering a recurrence. Each main group was then subdivided into children and adults and each subgroup again

according to whether the illness had been present for more or less than 14 days before admission. All the patients were kept in hospital for 42 days and regular detailed observations were made to determine progress [for details of these the original paper should be consulted], and all received aspirin for 14 days to control acute symptoms. In addition, half the patients in each group, randomly selected (the treated group), received intensive penicillin therapy for 42 days, consisting in 500,000 units sodium penicillin 4-hourly for 10 days, 600,000 units procaine penicillin twice a day for the next 11 days, and 1·2 mega units benzathene penicillin on the 22nd day. At the end of the 42 days all patients received 1·2 mega units benzathene penicillin intramuscularly, this being repeated every 5 to 6 weeks for 10 to 14 months. At each subsequent visit the observations were repeated and at the end of 12 months the cardiac status was evaluated.

Detailed analyses of the results, which are discussed at length subgroup by subgroup, showed no significant difference in the acute course of the disease between patients receiving intensive penicillin therapy and those given no antibacterial therapy. However, at the end of 12 months, when those patients in whom there was evidence of antecedent cardiac valvular disease at the time of admission were excluded (27), comparison of the remaining patients showed that valvular disease of the heart was 2½ times more frequent in the control group than in the treated group. It is suggested that the disparity between the effects of penicillin therapy on the acute manifestation of acute rheumatism and on the cardiac valvular lesions indicates that these two aspects of the disease may differ in pathogenesis, and that the valvular lesions may result from the presence and persistence of the haemolytic streptococci in the valves of the heart.

[This paper was published simultaneously in *Revista Médica de Chile*.] *C. Bruce Perry.*

Clinical Course of Rheumatism in Early Childhood. [In Russian.] ANDREYEVA, V. S. (1959). *Pediatrija*, 8. 10 refs.

Of 1,693 children aged 1 to 16 years with acute rheumatism observed during the 7 years 1950-57, 36 (2·1 per cent.) were under 3 years old. Of these 36 (22 boys, 14 girls), three (9 per cent.) had a history of previous attacks compared with 748 (44 per cent.) in the whole series. It thus appears that acute rheumatism at this early age is not so uncommon as is generally supposed and that, contrary to experience in older children, it may affect boys predominantly.

Home conditions were satisfactory in all but one of these 36 cases. There was a family history in six cases (16·6 per cent.)—a low figure. All the patients were full-term infants with a satisfactory birth weight who had been breast-fed to the 5th or 6th month. The attacks usually followed catarrh of the upper respiratory tract, influenza, or influenzal pneumonia. Five of the 36 developed pancarditis and nine died. Of ten whose primary attack occurred before the end of their second year, five died. The mortality among children under 2 was 50 per cent., among those aged 2 to 3 17·4 per cent., and among those aged 3 to 7 11·5 per cent., whereas in the rest of the series (age 7 to 16) it was 0·8 per cent. The commonest clinical picture of the disease in children under 3 years old was carditis with limb pains or polyarthritis. In no case were there symptoms of chorea.

L. Firman-Edwards.

Short-term Hormone Therapy: Its Effect in Active Rheumatic Carditis of Varying Duration. WILSON, M. G., and WAN NGO LIM (1959). *New Engl. J. Med.*, **260**, 802. 1 fig., 15 refs.

In a previous paper from the New York Hospital-Cornell Medical Center (*J. Amer. med. Ass.*, 1956, **160**, 1457; *Abstr. Wld Med.*, 1956, **20**, 384) it was reported that, when 55 attacks of active rheumatic carditis of 3 to 21 days' duration were treated with steroids for an average of only 7 days with early ambulation, there was no overt cardiac disease in most cases for an average follow-up period of 9 years, these results being in marked contrast to those obtained in 165 cases treated without steroids.

In the study herein reported a further 53 attacks of active rheumatic carditis in 46 patients (mostly children) were treated, after several days of initial observation and investigation, with various steroid hormones of the cortisone group, again for an average period of 7 days. The exact daily dose was determined by the circulating eosinophil count, the aim being to keep this below 10 per c.mm. The diagnostic criteria of active carditis were those of the American Heart Association, 26 of the attacks being presumably initial and 27 recurrent. The duration of the carditis before treatment was 4 to 21 days in 36 cases and 22 days to 4 months in seventeen. The clinical picture in most cases indicated severe disease. Improvement was generally rapid and impressive, particularly in those patients treated early in the disease, and progressive symptoms of carditis were terminated in 91 per cent. Five patients suffered a relapse soon after stopping treatment, but were re-treated with good response. Of 36 patients with initial attacks who were treated early, all but two recovered without overt cardiac damage. In the seventeen patients whose treatment was started late, progressive disease was prevented, although cardiac damage present at the onset of treatment was not reversed. Rebound phenomena without carditis were common on withdrawing steroid therapy (fourteen cases). The average daily dose of hydrocortisone was 320 mg. and of prednisone, prednisolone, and methylprednisolone 100 to 160 mg.

It is suggested that when the duration of the disease is less than 3 weeks, short-term steroid therapy results in the termination rather than the suppression of the clinical signs and symptoms of active carditis, and that long-term hormone therapy is not required in such cases. Rebound phenomena (as opposed to relapse of the carditis) do not require further treatment.

[The results obtained with treatment of such exceptionally short duration are remarkable.] *John Lorber.*

Rheumatic Heart Disease associated with Atrial Septal Defect: Clinical and Pathologic Study of Twelve Cases of Lutembacher's Syndrome. ESPINO-VELA, J. (1959). *Amer. Heart J.*, **57**, 185. 6 figs, 42 refs.

The author reports from the National Institute of Cardiology, Mexico City, twelve cases of mitral valvular damage associated with a wide atrial septal defect (A.S.D.), eleven of which were confirmed at necropsy and one at operation. Since 40 per cent. of all patients admitted to the Institute have rheumatic heart disease and since A.S.D. is the second most common congenital abnormality seen there, the author expresses surprise that this combination of lesions has not been found more often; indeed, only once in 500 commissurotomies has it been discovered at operation, although the atrial septum is regularly explored.

The patients were eight females aged 14 to 71 years and four males aged 10 to 48 years. Rheumatic heart disease was usually predominant, and there was a definite history of rheumatic fever in five cases and a doubtful one in two; but the presence of A.S.D., while always apparent from auscultatory, fluoroscopic, and cardiographic findings, was in three cases the more obvious lesion. Mitral valvular involvement was diagnosed in nine cases, tricuspid valvular disease in nine, and aortic incompetence in one; one patient had coarctation of the aorta. Cyanosis, due to pulmonary hypertension, was an important pointer to the possible diagnosis in five cases. Cardiac catheterization in two cases showed relatively high left atrial and pulmonary venous pressures. The disease progressed with increasing dyspnoea, haemoptysis occurring in six cases, and eventually nine patients died in congestive heart failure, one from renal failure due to therapeutic misadventure, and one immediately after operative closure of the A.S.D.; only one patient survives, in mild chronic failure.

Post-mortem examination showed that the heart was always large, weighing from 470 to 540 g. The most dilated cavity was the right atrium, followed in order of dilatation by the right and then the left ventricle, the latter being only slightly enlarged or even occasionally normal. In nine cases the septal defect measured between 15 and 60 mm. in diameter, but in the remaining three there was virtually a single atrium. Double mitral lesions, in which, however, stenosis predominated, were present in all cases. Tricuspid involvement was confirmed in seven cases and aortic damage in three; one case showed old pulmonary infarcts. Discussing this series, the authors stress that the co-existence of haemoptysis with severe chronic dyspnoea indicates venous capillary hypertension. They do not agree with the theory that A.S.D. is a protective mechanism against pulmonary hypertension in patients with mitral valvular disease. They accept Lutembacher's explanation for the atypical character of the diastolic murmur, but point out that their cases had other valvular lesions, differentiating them from true Lutembacher's syndrome. The radiological and cardiographic findings are also discussed. *R. S. Stevens.*

Current Status of Therapy in Rheumatic Fever. MCEWEN, C. (1959). *J. Amer. med. Ass.*, **170**, 1056.

Early Mobilization of Patients with Acute Rheumatism. (Frühzeitiges Aufstehen bei Kranken mit Rheumatismus acutus.) NASSAU, E., and ARON, A. (1959). *Ann. paediat. (Basel)*, **193**, 101. 3 figs.

Sulphonamides in the Prophylaxis of Rheumatic Fever. (L'impiego dei sulfamidici nella profilassi della malattia reumatica.) CHIEREGO, G. (1959). *G. Clin. med.*, **40**, 951. 2 figs, 32 refs.

Chronic Articular Rheumatism
(Rheumatoid Arthritis)

Triamcinolone in Rheumatoid Arthritis. ROBINSON, C. E., and ROBINSON, H. S. (1959). *Canad. med. Ass. J.*, **80**, 245. 2 refs.

A total of fourteen patients with rheumatoid arthritis or spondylitis received triamcinolone therapy over periods of 2 to 8 months. In this small series disturbing weight loss, progressive in some instances, occurred in ten cases. It is apparent that, in addition to the well-known side-effects of corticosteroids, new problems may occur with this steroid, including weight loss, headache, dizziness, and fatigue. Some of the new side-effects described may be sufficiently severe to preclude its use in long-term maintenance dosage. [*Authors' summary.*]

Preliminary Study of Iproniazid in Rheumatoid Arthritis. COKE, H., FURBER, S. E., and KERR-TAYLOR, H. (1959). *Rheumatism*, **15**, 2. 27 refs.

Two important features of rheumatoid arthritis are muscle weakness with wasting and the close relationship of the inception and course of the disease to psychological stress. As iproniazid has been reported to have a beneficial effect on both these features the authors have carried out a preliminary trial with this drug at the Charterhouse Rheumatism Clinic, London. Iproniazid inhibits mono-amine oxidase enzyme systems. Serotonin, histamine, and noradrenaline are all mono-amine substances and their breakdown is inhibited by iproniazid. It has also been shown *in vitro* that iproniazid diminishes the haemagglutination titre of the serum of patients with rheumatoid arthritis.

The drug was given to 26 ambulant out-patients with rheumatoid arthritis accompanied by muscle wasting and mental depression in a dose of 150 mg. a day in three divided doses, aspirin and the vitamin-B complex being also given. Eleven patients were unable to take the drug for longer than 2 weeks and showed symptoms of hyperexcitability of the nervous system, which passed off as soon as the drug was discontinued. The remaining fifteen cases were observed for periods of 2 months to one year. Any beneficial effect was noted within 10 days of taking the drug. Such effect consisted mainly in a great improvement in the depressive state accompanying the disease, and in some cases gain in weight and im-

proved functional capacity. There was, however, no certain evidence of any effect of the drug on the disease process itself, but its beneficial effect in relieving the depression that so frequently accompanies rheumatoid arthritis makes the drug a useful one in certain selected cases. The average weight gain in eleven patients was 1 lb. 8 oz. (680 g.) per patient per month.

G. S. Crockett.

Effects of Simultaneous Short-Term Administration of Corticotrophin and Cortisone Acetate in Patients with Rheumatoid Arthritis. [In English.] KALLIOMÄKI, J. L., KULONEN, M., and VASAMA, R. I. (1959). *Acta endocr.* (*Kbh.*), **31**, 49. 3 refs.

In studies carried out at the University Medical Clinic, Turku, Finland, the authors compared the pharmacological effect of cortisone alone with that of cortisone combined with corticotrophin (ACTH) in patients with rheumatoid arthritis. Of the 21 patients studied, ten (Group 1) were given 50 mg. cortisone daily, together with 25 units ACTH intramuscularly for 10 days, while the other eleven patients (Group 2) received 50 mg. cortisone only.

Of the ten patients in Group 1, the joint symptoms were improved in five and unchanged in five, while in Group 2 these symptoms were improved in four and unchanged in seven. No other effects on the course of the disease were observed. The erythrocyte sedimentation rate fell in both groups and the lower rate was maintained for one week after treatment in Group 1. The body weight of patients in Group 2 increased for a day or two at the beginning of treatment, but then returned to the basal values by the 10th day; in Group 1 there was no change in body weight. There was no significant change in the serum sodium and glucose levels in either group but the serum potassium level fell slightly in Group 2. No effect on the blood pressure was noted. The eosinophil count fell in both groups and remained low for more than 3 days after cessation of therapy, and in this respect also there was no significant difference between the two groups. The authors conclude [nevertheless] that they "feel justified in considering that . . . ACTH and cortisone acetate administered simultaneously yield effects which are unlike those of cortisone acetate given alone".

William Hughes.

Long-term Use of Prednisone and Prednisolone in Juvenile Rheumatoid Arthritis: Report of Fifteen Cases. HARNAGEL, E. E. (1959). *A.M.A. J. Dis. Child.*, **97**, 426. 22 refs.

At Los Angeles Orthopaedic Hospital prednisone and prednisolone were given to fifteen patients with juvenile rheumatoid arthritis, treatment lasting 8 to 24 months (average 19 months). Ancillary measures, such as physiotherapy and administration of aspirin, were continued, but no new methods of treatment were introduced. Since the anti-rheumatic action of the two drugs is similar they were used interchangeably in this study and were given in full dosage (nine of the patients being maintained on more than 10 mg. per day).

There was complete remission in three patients during the period of observation (two of whom had had remissions in the past) and some degree of improvement in six others. The remaining six patients were either not improved or became worse. However, twelve patients reported subjective relief. Side-effects were numerous, 28 being encountered, but they were largely of a minor nature and did not call for any modification in treatment. Transitory diabetes mellitus was reported in one case. There was some evidence that normal growth and increase in weight were slowed down during treatment.

The author concludes that the findings provide no evidence that these hormones alter the natural course of the disease or retard progressive joint damage, but subjective benefit was striking, while the minor side-effects which occurred did not present a serious problem.

B. E. W. Mace.

Studies of Adrenal Cortical Activity in Patients with Rheumatoid Arthritis: the Diurnal Pattern and Twenty-four Hour Levels of Urinary Total 17-Hydroxycorticosteroids and 17-Ketosteroids. HILL, S. R., HOLLEY, H. L., ULLOA, A., STARNES, W. R., HIBBITT, L. L., and MCNEIL, J. H. (1959). *Arthr. and Rheum.*, **2**, 114. 3 figs, bibl.

This paper from the University of Alabama reports a comparative study of the diurnal pattern and 24-hour total of urinary excretion of 17-hydroxycorticosteroids (17-(OH)CS) and 17-ketosteroids (17-KS) in ambulatory and hospitalized patients with rheumatoid arthritis and control subjects. The mean rate of 17-(OH)CS excretion (measured in 6-hour periods) in ten ambulatory normal subjects was highest between 7 a.m. and 1 p.m. and lowest from 1 p.m. to 7 p.m. This was also the case in eleven hospitalized normal subjects and in ten hospitalized patients with non-rheumatic chronic diseases. In contrast twelve hospitalized and eleven ambulatory patients with rheumatoid arthritis showed little variation in the rate of 17-(OH)CS excretion throughout the day and night. The mean 24-hour excretion of 17-(OH)CS in the two groups with rheumatoid arthritis was considerably less than in the normal and non-rheumatic groups, though it was considered to be within the normal range. The constant diurnal pattern of 17-(OH)CS excretion found in the patients with rheumatoid arthritis was not observed with 17-KS, excretion of which decreased from morning to evening in all groups. The mean 24-hour 17-KS excretion was remarkably constant in all groups and fell well within the normal range in the patients with rheumatoid arthritis.

The flattened diurnal pattern of 17-(OH)CS excretion and the high ratio between total 17-KS and 17-(OH)CS excretion in patients with rheumatoid arthritis as compared with control subjects are of considerable interest. The authors point out that speculation on a possible cause and effect is unwarranted at this time, but that the quantitative relationship of one hormone to another may be as important as the absolute level of either hormone alone.

Oswald Savage.

Comparison of the Latex Fixation-Whole Serum, Latex Fixation-Euglobulin Fraction, and Bentonite Flocculation Tests in the Laboratory Diagnosis of Rheumatoid Arthritis. HOLLEY, H. L., ULLOA, A., HENRY, M., GRIFFIN, S., and JOHNSTON, M. L. (1959). *Amer. J. med. Sci.*, **237**, 345.

Several serological tests have been described in recent years as aids in the diagnosis of rheumatoid arthritis; all are based on the presence in the serum of a protein of high molecular weight, associated with the γ-globulin fraction and known as the "rheumatoid factor". In this study, carried out at the Veterans Administration Hospital, Birmingham, Alabama, the authors have compared three such tests, namely, the latex fixation test using whole serum as described by Singer and Plotz, the latex fixation test using the euglobulin fraction as described by Craig, Kerby, and Persons (*J. Lab. clin. Med.*, 1957, **49**, 635), and the bentonite flocculation test of Bozicevich *et al.* (*Proc. Soc. exp. Biol. (N.Y.)*, 1958, **97**, 180; *Abstr. Wld Med.*, 1958, **24**, 212). Each test was performed on the sera of:

(1) 76 patients aged 19 to 72 years with a clinical diagnosis of rheumatoid arthritis (fulfilling the criteria of the American Rheumatism Association (A.R.A.), apart from the finding of a positive agglutination reaction);

(2) Nine patients with "atypical rheumatoid arthritis", that is, with a disease clinically suggestive of rheumatoid arthritis but not fulfilling the criteria of the A.R.A.;

(3) 71 patients with musculoskeletal disease other than rheumatoid arthritis, these being divided into eleven separate diagnostic categories.

The whole-serum latex-fixation method gave a positive result in 56 (74 per cent.) of the 76 patients with definite rheumatoid arthritis. A difference in the sex incidence was noted, 81 per cent. of the men but only 69 per cent. of the women giving a positive reaction, suggesting perhaps that a separate disease mimicking rheumatoid arthritis may occur in middle-aged women. None of the patients with atypical rheumatoid arthritis (Group 2) and only one in Group 3 (a patient with systemic lupus erythematosus) gave a positive result with this test.

The latex-fixation test using euglobulin gave a positive result in 86 per cent. of the 76 patients in Group 1, a negative result in all in Group 2, while in Group 3 only two patients (one with systemic lupus erythematosus and one with Sjögren's syndrome) showed a positive reaction. Lastly, with the bentonite flocculation test a positive result was obtained in 88 per cent. of cases in Group 1, in none in Group 2, and in only four cases (two of systemic lupus erythematosus and two of the "shoulder-hand syndrome") in Group 3.

The authors state that those patients with definite rheumatoid arthritis who showed no agglutinating activity by any of the three tests are being subjected to a latex-inhibition test which may reduce the size of this group. The significance of the reactions is discussed and the present results compared with those of other workers. It is of interest that in this series all three tests of agglutinating activity were negative in patients with osteoarthritis, ankylosing spondylitis, gout, Reiter's syndrome, Still's disease, scleroderma, "infectious arthritis", and rheumatic fever. *I. Berkinshaw-Smith.*

Peripheral Neuritis of Rheumatoid Arthritis. (Les névrites périphériques de la polyarthrite chronique évolutive.) VIGNON, G., and DURANT, J. (1959). *Sem. Hôp. Paris*, **28**, 2072. 36 refs.

The authors, working in Lyon, France, observe that the peripheral neuritis which complicates rheumatoid arthritis is rare, though upwards of forty cases have been reported in the literature in 1933, and they have personally recognized three cases. It occurs most frequently in longstanding and severe cases of rheumatoid arthritis. The mean duration of the arthritis was 8 years and in only one case was it less than 1 year before neuritis set in. Previous treatment with hormones was mentioned in all except two cases. The dosage was often high and in some cases withdrawal was abrupt. Gold had also been used in the majority of cases. In one of their three personal cases, the neuritis which had been improving, relapsed after injections of copper. The neuritis is usually multiple and asymmetrical in distribution, and is a mixed neuritis with sensory, motor, and trophic effects. There is paralysis with pain and muscular atrophy in the distribution of the affected nerve. Involvement of a cranial nerve is rare, but such cases have been described. Vascular lesions of many kinds included cerebral and coronary thrombosis, purpura, and gangrene of the extremities. The prognosis was not good, a fatal issue being recorded in eighteen out of the forty cases recorded. Pure neural lesions, which included demyelination of the peripheral nerves and degeneration of the posterior columns, were recorded in only one case. In all cases the typical lesions of periarteritis nodosa were found. The distribution of lesions is widespread and the arteries of the peripheral nerves and the voluntary muscles are constantly affected. Discussing the pathogenesis, the authors point out that periarteritis nodosa occurs in other forms of collagenous disease, including malignant hypertension, Buerger's disease, and temporal arteritis. They consider that cortisone is an aetiological factor of importance. No particular line of treatment has yet been proved effective, and the authors advocate absolute rest, sedation, and the graduated withdrawal of steroid treatment. Prevention is more important and hormones should be given with care and withdrawal should never be abrupt.

William Hughes.

Serum Responses in Rheumatoid Arthritis. [Review Article.] VAUGHAN, J. H. (1959). *Amer. J. Med.*, **26**, 596. 4 figs, bibl.

Prevention of Invalidism in Rheumatoid Arthritis: Active Immobilization. (Profilaxis de la invalidez en la artritis reumatoidea: inmovilidad activa.) KELLY, M. (1959). *Arch. argent. Reum.*, **22**, 1. 7 figs, 16 refs.

Effectiveness of Splinting and Bracing in Rheumatoid Arthritis. RHINELANDER, F. W. (1959). *Arthr. and Rheum.*, **2**, 270. 6 figs, 3 refs.

Systemic Rheumatoid Arthritis. EISENSTADT, H. B., and WALLACE, S. M. (1959). *Tex. St. J. Med.*, **55**, 576. 7 figs, 10 refs.

Arthroplasty of the Hip in Rheumatoid Arthritis. SCHWARTZMANN, J. R. (1959). *J. Bone Jt Surg.*, **41A**, 705. 21 figs.

Rheumatoid Synovial Cyst of the Hip. COVENTRY, M. B., POLLEY, H. F., and WEINER, A. D. (1959). *J. Bone Jt Surg.*, **41A**, 721. 10 figs, 11 refs.

Use of Synthetic Antimalarials in the Treatment of Rheumatoid Arthritis. (L'emploi d'antipaludiques synthétiques dans le traitement de la polyarthrite chronique évolutive.) KUIPERS, R. K. W. (1959). *J. belge Méd. phys. Rhum.*, **14**, 89. 8 refs.

Psychosocial Studies of Rheumatoid Arthritis: Parental Factors compared in Cases and Controls. KING, S. H., and COBB, S. (1959). *Arthr. and Rheum.*, **2**, 322. 10 refs.

Septic Complication of Rheumatoid Arthritis, with Particular Reference to Corticosteroid Therapy. (Septische Komplikationen bei Polyarthritis chronica, speziell unter Corticosteroidtherapie.) SCHÄFER, R. (1959). *Schweiz. med. Wschr.*, **89**, 911. 4 figs, 35 refs.

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(Osteo-Arthritis)

Ageing and Osteo-Arthritis of the Human Sternoclavicular Joint. SILBERBERG, M., FRANK, E. L., JARRETT, S. R., and SILBERBERG, R. (1959). *Amer. J. Path.*, **35**, 851. 20 refs.

Frequency of Radiological Signs of Lumbar Osteo-Arthritis in Osteo-Arthritis of the Hip in General and in the Primary Form in Particular. (Considérations sur la fréquence des signs radiologiques d'arthrose lombaire dans la coxarthrose en général et dans la coxarthrose primitive en particulier.) VERHAEGHE, A., LEBEURRE, R., CORNILLE, C., JACQUIEZ, J., and VITOU-VILLENEUVE, L. (1959). *Rev. Rhum.*, **26**, 266.

Synovial Tissue in Osteo-Arthritis of the Knee. HOULI, J., ROIMICHER, S., PACIORNIK, I., and DE PAOLA, D. (1959). *Acta rheum. scand.*, **5**, 122. 11 figs, 10 refs.

Experience with Tuberculin Therapy in Osteo-Arthritis. (Une expérience de tuberculinthérapie des arthroses.) FRANCKSON, J. (1959). *J. belge Méd. phys. Rhum.*, **14**, 94. 7 refs.

Erosive and Destructive Forms of Lumbar Osteo-Arthritis (Pseudo-Pott's Disease). (Les formes érosives et géodiques "Pseudo-Pottiques" de l'arthrose lombaire.) DE SÈZE, S., GUERIN, C., and RAMEAU, Mme (1959). *Rev. Rhum.*, **26**, 161. 9 figs, 4 refs.

Prophylaxis of Osteo-Arthritis. (Die Prophylaxe der Arthrosen.) TAILLARD, W. (1959). *Dtsch. med. Wschr.*, **84**, 1478. 4 figs, 23 refs.

(Spondylitis)

Heredity in Ankylosing Spondylitis. O'CONNELL, D. (1959). *Ann. intern. Med.*, **50**, 1115. 1 fig., 10 refs.

After a brief review of the literature concerning the hereditary factor in ankylosing spondylitis, the author reports an investigation of the incidence of ankylosing spondylitis and rheumatoid arthritis among the parents and siblings of seventy spondylitic patients attending Charing Cross Hospital, London. Among the 428 close relatives of the patients, sixteen with spondylosis were discovered. This incidence of roughly 1 in 27 among relatives of patients is far higher than previous estimates of the disease in the general population.

The family pattern of distribution of the spondylitis favoured transmission by a simple dominant gene with differing penetrance for males and females. Thus, among the 35 close relatives of nine female spondylitic patients, there were four cases of ankylosing spondylitis, which would seem to support a previous suggestion of greater penetrance in families with an affected mother or other female progenitor. In addition, six cases of rheumatoid arthritis were found among the 428 close relatives of the patients, an incidence of 1 in 71. The author notes that although this is twice or three times the estimated incidence of rheumatoid arthritis in the general population, the difference is not statistically significant. In one family the finding of the transmission of ankylosing spondylitis from grandfather to grandson through a rheumatoid mother strongly suggests a common genetic factor for the two diseases. *M. Wilkinson.*

(Miscellaneous)

Sacro-iliitis in Reiter's Disease. OATES, J. K., and YOUNG, A. C. (1959). *Brit. med. J.*, **1**, 1013. 21 refs.

The incidence of radiographic evidence of sacro-iliac joint disease in a series of 78 patients (76 men and two women) [ages not stated] who were treated at the London Hospital for Reiter's disease was studied. All the patients had arthritis in one or more [unspecified] joints, with urethritis and sometimes conjunctivitis or iritis. In 46 cases the patient had had more than one attack. The criteria whereby the *x*-ray findings were assessed are stated [although the number of observers is not specified and the use of a "blindfold" technique is not mentioned].

The sacro-iliac joints were regarded as normal in 34 cases and abnormal in 35 (unilateral in six and bilateral in 29); there was doubtful evidence of sacro-iliitis in nine cases. Of the 35 patients with definite radiographic evidence of sacro-iliitis, sixteen complained of backache and twelve had iritis, the average duration of the disease in this group being 13 years. In contrast, of the 34 patients in whom no such evidence was found, only five complained of backache and three had iritis, while the average duration of their disease was 4·8 years. All the patients with sacro-iliitis who were examined had genital infection in the form of chronic prostatitis, and the authors discuss the strong but inconclusive evidence for the role of focal infection in the causation of this condition and others affecting the joints of the spine and pelvis.

The occurrence of iritis in association with rheumatic diseases, particularly ankylosing spondylitis, has frequently been reported. Of the twelve patients with iritis in the group with sacro-iliitis, nine had recurrent attacks, a point which the authors stress. All showed evidence of prostatitis. The difficulty of distinguishing patients with Reiter's disease and sacro-iliitis from those with ankylosing spondylitis and iritis, and less commonly dysuria, are discussed. *J. Warwick Buckler.*

Comparative Radiological Study of Reiter's Disease, Rheumatoid Arthritis, and Ankylosing Spondylitis. MASON, R. M., MURRAY, R. S., OATES, J. K., and YOUNG, A. C. (1959). *J. Bone Jt Surg.*, **41B**, 137. 25 figs, 17 refs.

Of the 53 patients with Reiter's syndrome previously reported (Murray *et al.*, *J. Fac. Radiol.* (*Lond.*), 1958, **9**, 37; *Abstr. Wld Med.*, 1958, **24**, 238) the authors, working at the London Hospital, have compared the radiological findings in 25 with the corresponding findings in 81 cases of rheumatoid arthritis and 38 of ankylosing spondylitis. In all cases radiographs of the hands, feet, ankles (including the calcaneum), and pelvis were examined. Although the condition could not be differentiated radiologically in every case the following features were considered to be of value:

(1) In Reiter's disease exuberant periosteal new bone formation on the plantar surface of the calcaneum was considered to be characteristic. (A critical re-examination of three patients with rheumatoid and two with ankylosing spondylitis showing this feature indicated that in these cases the initial diagnosis was beyond suspicion in only one, and in this one case it was thought that Reiter's disease was present as well.) Of the patients with Reiter's disease this sign was noted in 20 per cent. Similar, but less marked changes may be observed round the wrist. Destructive joint lesions are common in the feet, but rare in the hands. Sacro-iliitis occurred in 32 per cent. and became more common with increasing duration of the disease, but unlike the other lesions it was usually symmetrical. Generalized osteoporosis was not a customary feature in this disease.

(2) In the radiographs of patients with rheumatoid arthritis the usual findings were confirmed. Peripheral arthropathy was slightly more common in the hands than in the feet and was accompanied by generalized osteoporosis. Sacro-iliitis did occur in 12 per cent. of these cases, but was later in onset and always less severe than in the following group.

(3) Ankylosing spondylitis. Here the predominant and early involvement of the sacro-iliac joints, observed in all cases, was found to be associated with peripheral arthropathy in the feet in 24 per cent. and in the hands in only 11 per cent. of these patients.

In all three conditions, posterior erosions of the calcaneum were sometimes seen and periosteal new bone formation was common round the malleoli.

Useful tables of distribution of the lesions in these conditions are given. Attention is also drawn to the age distribution; thus ankylosing spondylitis is earlier in onset, on the whole, than is rheumatoid arthritis, while Reiter's disease was found to occur in patients between the ages of 15 and 75, with its highest incidence in the fourth and fifth decades. *R. O. Murray.*

A Study of Reiter's Syndrome based on Eighty Cases observed in Tunisia. (Le syndrome de Fiessinger-Leroy-Reiter; enseignments fournis par l'étude de 80 cas observés en Tunisie.) MASBERNARD, A. (1959). *Rev. Rhum.*, **26**, 21. 1 fig., 36 refs.

The author reports eighty cases of post-dysenteric Reiter's syndrome occurring in military personnel in Tunisia. The incidence of the syndrome followed closely the incidence of dysentery from June to December and affected mainly young men who had arrived recently from France. Urethritis, mostly abacterial in nature, was present in 80 per cent., eye involvement in 94 per cent., and arthritis in 96 per cent. of the cases observed. The arthritis affected mostly the lower limbs, especially the knees. In the more severe cases marked muscular wasting, particularly of the quadriceps femoris, became one of the most intractable features of the syndrome. In four cases there were transient cardiac murmurs, with abnormal electrocardiographic findings. There was a well-marked increase in the α_2-globulin fraction of the serum proteins in no less than 94 per cent. of cases; a rise in the γ-globulin level was found in 60 per cent. of cases.

Aureomycin appeared to prevent later complications, such as ankylosing spondylitis, if given early; once the syndrome was well established, however, antibiotics proved ineffective.

Diacetylpyrocatechol given in combination with prednisone was found to be the most effective treatment of the established condition. *G. W. Csonka.*

The Hands in Arthritis. CRAIN, DARRELL C. (1959). *J. Amer. med. Ass.*, **170**, 795. 3 figs.

The author, writing from the Georgetown University Medical Center, Washington, D.C., divides the activities of the hands into three general categories: "gripping", "pinching", and "tapping". Cutting, for example, is a combination of the first two.

In early rheumatoid arthritis, the "spindle-shaped" appearance of the proximal interphalangeal joints may be obvious before any *x*-ray changes are seen. Later, the distal joints may become involved with narrowing of joint-spaces indicating cartilaginous destruction. Ulnar deviation is caused by the muscular pull of interossei and flexor muscles, in the presence of damaged metacarpophalangeal joints. There may also be ankylosis and resorption of epiphyseal bone.

In osteo-arthritis, the familiar Heberden node seen in middle-aged women may show only slight narrowing of the distal joint-space radiologically, and possibly slight lipping of the bone margin, but such nodes may become acutely inflamed without any additional changes on the *x*-ray film. Nodes may grow to a great size with evidence of cystic degeneration in the subchondral bone.

"Psoriatic arthritis" may, in its later stages, show severe rheumatoid deformities of the "opera-glass" type with chronic discoloration of the skin. Crippling deformities may be seen in gout and the well-known "punched-out" areas recognized on the films. Scleroderma may immobilize the hand by its contracting action. Similar restrictions may be seen in general calcinosis and one or two fingers may be affected in Dupuytren's contracture; in all three conditions *x* rays will demonstrate unaffected joints. Current methods of treatment are useful in limiting deformities and should be vigorously pursued, but the tendency to neglect massage is unjustifiable. *David Preiskel.*

Erythema Nodosum. A Study of Seventy Cases. VESEY, C. M. R., and WILKINSON, D. S. (1959). *Brit. J. Derm.*, **71**, 139. 3 figs, 40 refs.

After giving a brief outline of the historical background of erythema nodosum, which was first described by Willan in 1798, the authors analyse seventy consecutive cases in order to establish the relative incidence of the three main causes—namely, tuberculosis, streptococcal infection, and sarcoidosis. The cases fell into six main groups:

(1) Tuberculous—four cases—the oldest patient being aged 24 years;
(2) Streptococcal—eight "proved" and seventeen "presumed" cases—the main criteria being a preceding tonsillitis and the finding of β-haemolytic streptococci;
(3) Bilateral hilar-node syndrome without evidence of parenchymatous sarcoidosis—twenty cases, average age 32 years;
(4) Erythema nodosum with pulmonary sarcoidosis—five cases, average age 42 years;
(5) Middle-aged women with recurrent bronchitis—seven cases;
(6) Miscellaneous and unknown—nine cases.

Thus, of the seventy cases, 45·6 per cent. were of proven or presumptive streptococcal origin, 35·7 per cent. accompanied sarcoidosis, 13 per cent. were of mixed or unknown origin, and only 5·6 per cent. were tuberculous. The authors noted depression frequently in patients with disease of the sarcoid type.
E. W. Prosser Thomas.

Subacute Nodular Migratory Panniculitis. VILANOVA, X., and PIÑOL AGUADÉ, J. (1959). *Brit. J. Derm.*, **71**, 45.

Reporting from the University of Barcelona the authors present, in Tables, the clinical findings in nineteen patients (one male) with subacute nodular migratory panniculitis, a new disease entity, the first fourteen cases of which they described in an earlier paper (*Ann. Derm. Syph. (Paris)*, 1956, **84**, 369). The diversity of the clinical and histological features of the entity may account for the difficulty in identifying it.

All the patients had nodules and plaques, which were limited to the lower part of the leg, but the age at the time of onset varied from 16 to 65 years. In the differential diagnosis nodular vasculitis and erythema induratum may have to be considered, but the situation of the nodules in nodular migratory panniculitis and the absence of ulceration are distinctive. It was noted that eleven patients had acute tonsillitis before the onset of the condition. The histological findings are described (and illustrated in photomicrographs); the fundamental change was a capillaritis in the hypodermis, with the formation of a pseudo-foreign-body granuloma. Biopsy examination often enabled a definite diagnosis to be made. Treatment with potassium iodide caused some of the nodules to disappear.

[No information is given regarding the state of the circulation in the affected legs and whether or not there had been previous thrombophlebitis.] *S. T. Anning.*

Relief of Arthritic Pain and Rehabilitation of the Chronic Arthritic Patient by Extended Sympathetic Denervation. HERFORT, R., and NICKERSON, S. H. (1959). *Arch. phys. Med.*, **40**, 133. 23 refs.

Conventional lumbar sympathectomy has been tried occasionally in the past for the relief of arthritic pain, but a poor impression has been obtained of its efficacy. On fourteen patients with pain due to arthritis in the lower limbs the present authors have performed a more extensive operation, removing the lumbar sympathetic trunk on the side of the painful joint from the crus to the pelvic brim and interrupting sympathetic fibres crossing from the opposite side by making "cross-hatch" cuts on to the periosteum of the 3rd and 4th lumbar vertebrae. This has necessitated mobilizing the vena cava and the aorta. Post-operative sweating patterns have shown patchy areas of anhidrosis on the contralateral thigh,

suggesting that decussating fibres are in fact interrupted by this operation. In one additional case in which venous abnormalities prevented the removal of the upper lumbar trunk there was no relief of pain in the corresponding knee joint.

Brief case histories are given. Many of the patients were elderly; the oldest was 81 and the youngest 49 years old. Arthritic pain had usually been present for several years and steroid therapy had been tried without success. Intractable pain was [apparently] the only criterion for selection of the cases; vasomotor phenomena were not present. One patient had undergone obturator neurectomy and cordotomy with only temporary relief. There was no operative mortality or morbidity. All the patients reported relief of rest pain immediately on recovering from anaesthesia, with increasing mobility of the affected joint during the next 2 weeks. No relapse has occurred, the follow-up period ranging from 3 months to 3½ years. The authors believe that the operation interrupts pain fibres arising within the joints of the lower limb. *C. J. Longland.*

Antimalarials in the Treatment of Sjögren's Syndrome. HEATON, J. M. (1959). *Brit. med. J.*, **1**, 1512. 6 refs.

Since there is some evidence that Sjögren's syndrome is a form of systemic lupus erythematosus, the author treated 25 patients with malarials. Two drugs were used: chloroquine sulphate and hydroxychloroquine sulphate (Plaquenil). Eight patients failed to improve (three of these had toxic reactions which necessitated withdrawal of the drug before it could take effect).

Of the remainder there was a variable degree of improvement, after 4 to 8 weeks of treatment.

The author considers that the results of this clinical investigation suggest that further trials of antimalarials in Sjögren's syndrome "would be worth while". *C. A. G. Cook.*

Electromyographic Study of Patients with Arthritis. [In English.] GRAUDAL, H., and HVID, N. (1959). *Acta rheum. scand.*, **5**, 34. 1 fig., 16 refs.

At Rigshospitalet, Copenhagen, muscle action potential was studied by means of a three-channel electromyograph in 31 arthritic patients, most of whom had rheumatoid arthritis. At room temperature 138 potentials were recorded from the first dorsal interosseous muscle of the hand, the values being compared with those in ten healthy females, aged 19 to 22 years. In nineteen of the 31 patients there was a reduction in the duration of the potentials, which, the authors state, is characteristic of myositis and certain other forms of myopathy. In one instance the deviation from normal was as high as 35 per cent. The deviations were not attributable either to disuse atrophy or to a high intramuscular temperature, but serological tests appeared to show some relationship between the deviations and haemagglutination and streptococcal agglutination reactions. Electromyographic abnormalities were observed as early as one month after the onset of symptoms and before muscle atrophy had developed. They were not modified by gold or corticosteroid therapy.

In eleven patients the duration of action potentials was normal. Spontaneous activity was recorded in 18 cases, but the exact significance of this was difficult to determine. In one patient with ankylosing spondylitis the potentials obtained from the muscle in a state of relaxation resembled the fibrillation potentials associated with denervation.

It is of interest that in seventeen cases other muscles, such as the tibialis anticus, quadriceps extensor femoris, and opponens pollicis, were tested, and the responses were invariably normal. *A. Garland.*

Effect of Myocardial Infarction on the Articular Disorder in Rheumatoid Arthritis. (Wpływ zawału mięśnia serca na dolegliwości stawowe w gośćcu pierwotnie przewlekłym.)

Polyarthritic Disturbances in the Course of Myocardial Infarction. (Zmiany wielostawowe w przebiegu zawału mięśa serca.) JOCHWEDS, B. (1959). *Pol. Tyg. lek.*, **14**, 380 and 483. 21 refs.

In the first of these two papers a clinical study is presented of five patients with rheumatoid arthritis quiescent for at least a year who were admitted to hospital after an attack of myocardial infarction of moderate severity. In three cases the inflammation of the joints flared up within 12 to 18 hours of the onset of cardiac pain, while in the other two joint pains developed in the 2nd and 4th weeks respectively. Phenylbutazone in doses of 0·6 g. daily was effective in controlling the joint pains, aspirin and other analgesics being less useful.

The second paper deals with the occurrence of polyarthritis in association with myocardial infarction in patients who had never previously suffered from joint disease. (The classic "shoulder-hand" syndrome is not included in the series.) During the 3-year period 1954-57, six such cases were seen. In one case the joint symptoms preceded the myocardial infarction by one day, in a second case they developed on the same day, and in others they appeared between the 4th and 6th weeks after the infarction. In all cases the pains in the joints disappeared, usually without any special treatment, though in some they lasted 6 to 7 months. In only one case were there objective clinical and radiological changes characteristic of rheumatoid arthritis; even in this case recovery was complete. The pathogenesis is obscure, possible factors suggested by the author including hormonal disturbances, "stress", and the products of tissue necrosis.

[The abstracter has recently treated a middle-aged woman who, after a severe attack of myocardial infarction, had an acute exacerbation of long-standing rheumatoid arthritis. The affected joints were very painful and the usual analgesics appeared to have little effect. Improvement in the joints began after 10 to 14 days, coinciding with the improvement in the cardiac condition.] *A. I. Suchett-Kaye.*

Phenylbutazone and Its Derivatives with Special Reference to G.27202. DUDLEY HART, F., and BURLEY, D. (1959). *Brit. med. J.*, **1**, 1087. 16 refs.

The relatively high incidence of gastro-intestinal side-effects with phenylbutazone had led to a search for a

better tolerated derivative with similar pain-relieving activity. Such a derivative is hydroxyphenylbutazone (G.27202), which is identical with one of the two metabolites that can be isolated from the urine of patients receiving phenylbutazone, from which it differs in having a phenolic group in the para position of one benzene ring. It is readily absorbed from the gastro-intestinal tract, and with repeated daily oral administration the plasma level reaches a plateau after 3 days and thereafter remains constant. In a daily dosage of 800 mg. it causes significant retention of sodium and water in the body (as does an equivalent dose of phenylbutazone) but has no uricosuric effect. Animal experiments suggest that G.27202 has greater analgesic activity than phenylbutazone and less ulcerogenic effect.

The authors describe a clinical trial of G.27202 which was carried out at the Westminster Hospital, London. Of the 117 patients (52 male and 65 female) treated, 62 had rheumatoid arthritis, 25 ankylosing spondylitis, 26 osteo-arthritis, and four miscellaneous rheumatic conditions. The two drugs were given in equal doses (usually 100 mg. two, three, or four times daily with meals). All the patients received each drug for one to 3 weeks and were asked to state which (if either) was the more effective in relieving pain and stiffness. Records were also kept of side-effects due to the treatment and observations were made on fluid retention.

G.27202 was considered the more effective by 15 per cent. of the patients and phenylbutazone by 32 per cent.; 29 per cent. considered that the drugs were equally effective and 24 per cent. that neither was effective. Of the 89 patients who were helped by both drugs, 34 considered them to be equally effective, eighteen preferred G.27202, and 37 preferred phenylbutazone. Of this last group, fourteen patients were given G.27202 in increasing doses until an effect equivalent to that of phenylbutazone was produced. The effective dose ratio of G.27202 to phenylbutazone was 2 : 1 in five cases, 5 : 3 in one, and 3: 2 in eight. Many of the patients who preferred G.27202 were intolerant of phenylbutazone.

Of the 117 patients in the trial, 25 developed symptoms of gastric intolerance with phenylbutazone, which in twenty cases were so severe as to necessitate discontinuation of treatment. The corresponding figures for G.27202 were ten and four respectively. Evidence of fluid retention was found in three cases with phenylbutazone and five with G.27202. One patient developed pyrexia and an urticarial rash while taking G.27202 and two patients complained of giddiness and headache with both drugs. There was no evidence of leucopenia in any case. G.27202 was administered in doses of 300 to 400 mg. daily to fourteen patients for periods of 3 to 12 months without evidence of intolerance.

The authors emphasize that although these drugs relieve the pain of chronic rheumatism, they have no significant anti-inflammatory effect on swollen joints. They conclude that, in general, G.27202 has less pain-relieving activity than phenylbutazone, but is decidedly less liable to cause gastro-intestinal disturbance; it may therefore play a useful part in cases in which phenylbutazone is poorly tolerated. Further modification of the phenylbutazone molecule may produce less toxic and more useful compounds for the treatment of chronic rheumatic disorders. *P. T. Main.*

Stevens-Johnson Syndrome caused by Phenylbutazone—Results of Treatment with ACTH. (Ectodermosis erosiva pluriorificialis (sindrome Stevens-Johnson) por ingestion de fenilbutazona—resultado de tratamiento con la ACTH.) MUZZIO D'AMELIA, J. C., BALINA, L. M., NICOLL, C., and NALLAR, L. (1958). *Arch. Oftal.* (*B. Aires*), **33**, 79. 2 figs, 52 refs.

A p-Nitro Analogue of Phenylbutazone possessing Potent Antirheumatic Sodium-Retaining and Uricosuric Properties. YÜ, T. F., BURNS, J. J., DAYTON, P. G., GUTMAN, A. B., and BRODIE, B. B. (1959). *J. Pharmacol. exp. Ther.*, **126**, 185. 2 figs, 14 refs.

Results of Treatment with Phenylbutazone Calcium in Association with Prednisone in Rheumatology. (Resultados obitidos com o emprêgo da fenilbutazona cálcico associada a prednisona em reumatologia.) NEBÓ, F., SPILSBORGHS, G., and PAULO, S. (1959). *Rev. Ass. med. bras.*, **5**, 164. 6 figs, 8 refs.

Reiter's Syndrome *versus* Keratosis Blennorrhagica *sine* Blennorrhagica. ELLIS, F. A., and BERESTON, E. S. (1959). *Sth. med. J.* (*Bgham, Ala.*), **52**, 828. 1 fig., 10 refs.

Disk Syndrome

Usual Causes of Resistant Sciatica. (Causas poco frecuentes de lumbociaticas rebeldes.) PIQUÉ, J. A. (1959). *Rev. argent. Reum.*, **24**, 125.

Gout

Results of a Clinical Trial of G-28315, a Sulphoxide Analogue of Phenylbutazone, as a Urucosuric Agent in Gouty Subjects. YÜ, T. F., BURNS, J. J., and GUTMAN, A. B. (1958). *Arthr. and Rheum.*, **1**, 532. 2 figs, 14 refs.

The modern treatment of gout depends on increasing the loss of urates from the body by giving drugs which depress renal tubular reabsorption of filtered urate. The phenylbutazone derivative sulphinpyrazone ("anturan"; "G-28315") is such a drug. In this paper from Mount Sinai Hospital, New York, and the National Heart Institute, Bethesda, Maryland, the authors report their experiences with the clinical use of sulphinpyrazone in 44 patients with gout, of whom 42 were in the tophaceous stage, twelve had extensive deposits of urate, and eight had persistent pain and stiffness between attacks.

In 29 patients, the initial mean urate excretion per 24 hours was 509 mg., 25 of them showing a daily excretion of less than 600 mg. After they had been treated with sulphinpyrazone in a dosage of 400 mg. per day, the mean daily excretion rose to 839 mg., being over

600 mg. in 25 cases. In forty patients with an initial serum urate level over 7 (mean 10·7) mg. per 100 ml., this level fell to a mean of 7 mg. per 100 ml., 22 patients showing values below this. With the dosage of 400 mg. daily, however, only seven out of forty patients achieved normal serum urate levels (below 6 mg. per 100 ml.) and in some "resistant" patients the serum urate level fell further following an increase of the dosage to 600 or 800 mg. per day. Reduction in the size of visible tophi occurred in all but four of twenty patients followed up for over 7 months. Side-effects, mostly mild, occurred on eighteen occasions in twelve patients; these included dyspepsia and gastro-intestinal upset (five cases), renal colic and/or calculus (eight), and a flare-up of acute gouty arthritis (five). Insufficient time has elapsed to assess any long-term hazards. A combination of sulphinpyrazone and zoxasolamine had a synergistic action in one patient. Four illustrative case histories are presented to show that some patients were tolerant of sulphinpyrazone but intolerant of other uricosuric drugs and *vice versa*. The authors conclude that sulphinpyrazone is a useful addition to the several uricosuric drugs at present available. *Allan St. J. Dixon.*

Gout and Blood Dyscrasias. TALBOTT, J. H. (1959). *Medicine* (*Baltimore*), **38**, 173. 110 refs.

Gouty Arthritis. Current Concepts in Treatment and Control. TALBOTT, J. H. (1959). *Minn. Med.*, **42**, 1044. 4 figs, 8 refs.

Recent Findings on the Physiopathology of Gout. (Données récentes sur la physiopathologie de la goutte.) VILLA, L., ROBECCHI, A., and BALLABIO, C. B. (1959). *Rev. Rhum.*, **26**, 229. 7 figs, 47 refs.

Results of a Study of 100 Cases of Gout. (Résultats d'une étude de 100 cas de goutte.) DE SÈZE, S., RYCKEWAERT, A., LEVERNIEUX, J., and MARTEAU, R. (1959). *Sem. Hóp. Paris*, vol. 35, No. 34-35, No. 60-61, p. 2289.

Pararheumatic (Collagen) Diseases

Lupus Erythematosus treated with a Combination of Quinacrine, Hydroxychloroquine, and Chloroquine. TYE, M. J., WHITE, H., APPEL, B., and ANSELL, H. B. (1959). *New Engl. J. Med.*, **260**, 63. 16 refs.

A combination of "quinacrine" (mepacrine), hydroxychloroquine, and chloroquine was given to 45 patients with chronic discoid lupus erythematosus (L.E.) and three with subacute systemic L.E. seen at Boston City Hospital and in private practice between October, 1956, and January, 1958. The drugs were given in a tablet containing 25 mg. quinacrine, 50 mg. hydroxychloroquine, and 65 mg. chloroquine. A dosage of one tablet morning and evening was adequate in twenty patients, but thirteen required three tablets, six required four, and two required six tablets daily [*sic*]. Only one patient (with subacute systemic L.E.) required eight tablets a day before the response was adequate. There was complete clearing of the lesions in nineteen cases of chronic discoid L.E. and in one of subacute systemic disease, while the clearing was almost complete in nine further cases of chronic discoid L.E. Partial clearing (50 per cent. of the lesions completely healed) was obtained in sixteen cases of discoid L.E. and in two cases of the subacute systemic form. Generally, improvement became evident 2 to 4 weeks after the start of treatment. The authors point out that assessment of the value of treatment was based on objective improvement in the inflammation; the scars in L.E. cannot change. Of the twenty patients with complete clearing, thirteen relapsed but a remission was obtained and maintained with smaller doses than those given initially. Apart from minor gastro-intestinal disturbances in four cases, reactions severe enough to necessitate cessation of treatment occurred in six cases only—namely, skin reactions in three and an abnormal cephalin flocculation titre in three, in one of which there was associated blond discoloration of the hair. In one patient with psoriasis as well as chronic L.E., the psoriasis appeared to become worse with this treatment regimen.

It is concluded that this combination of antimalarial drugs may be more effective than any one of the drugs given alone, but that quinacrine ,"because of its tendency to produce skin reactions is the drug most likely to be displaced, in part or altogether, by either or both of the others". *E. W. Prosser Thomas.*

Role of Splenectomy in the Management of Acquired Autoimmune Haemolytic Anaemia complicating Systemic Lupus Erythematosus. SARLES, H. E., and LEVIN, W. C. (1959). *Amer. J. Med.*, **26**, 547. 3 figs, 25 refs.

An investigation of the part played by splenectomy in the management of acquired haemolytic anaemia is reported in this paper from the Hematology Research Laboratory, University of Texas, Galveston. The authors describe in detail three cases of systemic lupus erythematosus in which steroid therapy did not result in any improvement in an associated acquired haemolytic anaemia, but satisfactory remission followed splenectomy.

The rationale of the operation is discussed. Contrary to the findings of others splenectomy did not have any ill-effects on the course of the primary disease.

R. B. Thompson.

Lupoid Hepatitis and the Hepatic Lesions of Systemic Lupus Erythematosus. MACKAY, I. R., TAFT, L. I., and COWLING, D. C. (1959). *Lancet*, **1**, 65. 2 figs, 19 refs.

The authors report from the Royal Melbourne Hospital, Victoria, Australia, the findings in fourteen patients with lupoid hepatitis, this term being used to describe the condition in which patients with chronic hepatitis and cirrhosis also show a positive result in the lupus erythematosus (L.E.) cell test; nine of the ten female patients and two of the four males were below the age of 40. In five cases the initial illness resembled acute infective hepatitis, while two patients had chronic nutritional hepatitis due to alcoholism; in the remaining seven the jaundice developed insidiously and without apparent cause.

The hepatitis was unusually severe and progressive, with recurrent exacerbations of jaundice and sometimes episodes of hepatic failure. The liver and spleen were enlarged. Liver function tests were "profoundly disturbed", and the erythrocyte sedimentation rate (Westergren) was increased. The serum γ-globulin level was usually above 2 g. per 100 ml., a finding in itself suggestive of an immunological disorder. The plasma oxalacetic glutamic transaminase level was raised in eight out of nine patients tested, indicating the presence of liver-cell necrosis. Other systemic manifestations included joint pains (seven), rashes (four), renal lesions (three), ulcerative colitis (three), pleural effusion (two), and haemolytic anaemia, lymphadenopathy, myocarditis, and thrombocytopenia in one case each. The L.E. cell test usually gave a weakly positive result; in eight cases the test result was positive only once, but in the remaining six it was positive on several occasions, and in one case repeatedly. The auto-immune complement-fixation reaction was positive in nine out of ten patients tested. Of eleven patients treated with cortisone, four responded immediately, one had a moderate remission, four showed slight and sometimes transient improvement, but two showed no improvement. Liver biopsy was performed in twelve cases and necropsy in the eight fatal cases; the liver invariably showed both macroscopically and microscopically the characteristic appearances of active chronic hepatitis.

The incidence of histological lesions in the liver was assessed in a further nineteen patients with systemic lupus erythematosus. In nine of these the liver was enlarged, while minor liver changes were found in eleven patients, but in most cases were insufficient to give rise to clinical or biochemical manifestation. Typical chronic hepatitis was present in two of these patients.

In discussion the authors state that lupoid hepatitis differs from classic systemic lupus erythematosus in that hepatic disease is the initial and dominant feature throughout, but overlapping features in both groups suggest a similar pathogenesis, possibly mediated through abnormal immunological responsiveness with autodestruction (autoclasia) of host tissues. It is suggested that a closer study of cases of lupoid hepatitis "may provide clues as to why active chronic hepatitis pursues its relentless course". *J. Warwick Buckler.*

Disseminated Lupus Erythematosus. Analysis of 100 Cases treated with Adrenocorticoids and Comparison with 25 Untreated Cases. (Lupus eritematoso generalizado. Analisis de 100 casos tratados con corticoides suprarrenales y comparacion con 25 casos no tratados.) JALIL M., J., ARMAS CRUZ, R., HARNECKER J., J., and GONZALEZ, F. (1958). *Rev. méd. Chile*, **86**, 717. 23 refs.

In this study reported from the Hospital Salvador (University of Chile), Santiago, the clinical and laboratory findings in 100 patients with disseminated lupus erythematosus treated with corticosteroids were compared with those in 25 "untreated" patients seen before 1950. The groups were similar in regard to age at onset, and severity and mode of presentation of the disease. Between 1950 and 1955 cortisone, and from 1955 onwards prednisolone, were the drugs most frequently employed. The initial dose was 200 to 500 mg. per day of cortisone or its equivalent, while the maintenance dose ranged from 6·25 to 175 mg. per day. (Chloroquin and isohaemotherapy were also given in a number of cases.) Treatment was continued as long as practicable, this period being less than one year in 52 cases, 1 to 2 years in 26, and 2 to 7 years in 22. Patients showing only fixed discoid lesions were observed without treatment, but all others with evidence of disease activity, that is, rash, fever, fall of hair, blood changes, and a positive result in the L.E.-cell test, were treated in the hope of preventing the development of irreversible changes, such as nephrosis.

Of the 100 treated cases, 55 developed some degree of Cushing's syndrome; dyspepsia occurred in 27, but was controlled by changes of diet or dose or by alkalis; three patients suffered from peptic ulcer, which was fatal in two; hypertension developed in 22 patients, but could usually be controlled with hypotensive drugs; heart failure was a complication in twelve patients, in three of whom treatment had to be stopped; ten patients developed epilepsy, which in four cases was related to steroid treatment and responded to reduction of the dosage or withdrawal; six patients suffered from meningeal or miliary tuberculosis, demonstrated at necropsy in five. Only one patient developed uncontrollable pyogenic infection attributable to the corticosteroids. Adrenal crises were not observed. Osteoporosis and pathological fractures occurred, but the exact incidence was not known since these complications had not been systematically looked for. In the few patients who became pregnant the doses of corticosteroids were reduced and no ill effects on the mother or foetus were seen. Of the 25 untreated patients, 21 died, the mean survival period being 11·8 months from onset of disease; the other four were not traced, but were presumed to be dead. In contrast, the over-all mortality in the treated group was 50 per cent. and the mean survival time 30·9 months from onset among those who died. Comparison of various groups showed that survival was related to the promptitude and adequacy of treatment.

The authors re-affirm the especially bad outlook in this disease for patients with the nephrotic syndrome or nitrogen retention, or in cases with severe onset. They stress the need for constant supervision, both in hospital and after discharge, and for measures to ensure prompt readmission and treatment for complications. They conclude that in conjunction with general medical care, the advent of corticosteroids has considerably improved the prognosis in disseminated lupus erythematosus.

A. St. J. Dixon.

Relaxin ("Releasin") Therapy in Diffuse Progressive Scleroderma. A Preliminary Report. EVANS, J. A. (1959). *A.M.A. Arch. Derm.*, **79**, 150. 4 figs, 10 refs.

In a previous study of the results of all forms of treatment of diffuse progressive scleroderma, the author and colleagues found that extensive sympathectomy resulted in palliation in about 88 per cent. of patients. In an

attempt to help these patients still further, the present author, at the Lahey Clinic, Boston, tried administration of relaxin, a polypeptide-like ovarian hormone which occurs most abundantly during pregnancy. To a series of eleven patients (nine female and two male) who had been subjected to sympathectomy for widespread scleroderma, relaxin was given intravenously for "3 to 7 days in increasing doses from 2·5 to 80 mg. in 5 per cent. dextrose and saline solution", and then intramuscularly in a dosage of 30 to 50 mg. twice to seven times a week. Subsequently four of the patients received a rectal suppository containing 40 mg. daily. All the patients were given, in addition, 1 mg. of diethylstilboestrol daily throughout the trial.

In general there was greater flexibility of the skin in eight of the eleven cases treated for 7 to 23 months, the hands showing least improvement. Soreness at the injection site was common and in two patients a local allergy to the injections developed which was controlled by hydrocortisone. One patient had a fatal anaphylactoid reaction when an intravenous injection was repeated after suppositories had been used.

A further two patients received relaxin before sympathectomy: one became progressively worse, showing no improvement after the operation, and died from anaphylaxis; the other showed improvement only after operation. In a group of six patients treatment was begun some months after operation; in four of these there was definite improvement in sclerodermatous skin areas; the remaining two patients died—one some time later from a ruptured oesophagus and one from an unknown cause. Of three cases in which relaxin was given immediately after operation there was notable improvement in one and some improvement in non-sympathectomized areas in one; the third patient died after 4 months. Dysphagia was relieved in four out of eight patients with oesophageal scleroderma. Healing of long-standing ulcers of the leg was complete in two out of three patients; the third patient, however, benefited considerably from the treatment. *Benjamin Schwartz.*

Problem of Interrelation between Diffuse Generalized Scleroderma, Acrosclerosis, Raynaud's Phenomenon, and Raynaud's Disease. [In English.] ŠŤÁVA, Z. (1959). *Dermatologica*, **118**, 1. 10 refs.

The author reviews a series of seventy patients with diffuse scleroderma who were followed up for periods of 8 to 10 years at the Second Dermatological Clinic of Charles University, Prague. Raynaud's phenomenon was present in sixty patients (57 women, three men), its onset having preceded the onset of the scleroderma (by 2 to 34 years) in 41 cases and developed simultaneously with it in nineteen. It appeared that the earlier Raynaud's phenomenon develops and the shorter the interval between its onset and that of scleroderma, the worse the prognosis. In five cases rheumatoid arthritis of the hands preceded Raynaud's phenomenon and in fourteen cases the onset of rheumatoid arthritis and scleroderma coincided. All these cases proved to be serious, with rapid progression.

The author considers that "there is a very close relation between Raynaud's disease and scleroderma of the acrosclerotic type to the point of possibly being the same disease with different degrees of involvement".

I. McLean Baird.

Honeycomb Lungs and Malignant Pulmonary Adenomatosis in Scleroderma. CAPLAN, H. (1959). *Thorax*, **14**, 89. 10 figs, 32 refs.

Two cases of scleroderma associated with cystic changes in the lungs and pulmonary adenomatosis are described [from Whittington Hospital, London]. In Case 1 the adenomatosis was possibly malignant, in Case 2 it was unequivocally so with metastases to pleura and diaphragm.

The appearances of cystic fibrosis of the lungs found in association with scleroderma are discussed. It is considered that these changes show no essential difference from those found in honeycomb lung and that the pulmonary fibrosis of scleroderma is similar to other pulmonary fibrosis or granulomata in being the antecedent of honeycomb lung.

The relation of "tumourlets" and pulmonary adenomatosis to carcinoma and the pathogenesis of hyperplastic respiratory epithelium are discussed. The hypothesis is put forward that the hyperplastic epithelial changes are in some way related to impaired respiratory function associated with increased pulmonary fibrosis.—[*Author's summary.*]

Cardiac and Renal Manifestations in Progressive Systemic Scleroderma. ROTTENBERG, E. N., SLOCUMB, C. H., and EDWARDS, J. E. (1959). *Proc. Mayo Clin.*, **34**, 77. 3 figs, 5 refs.

Nine patients with generalized scleroderma were studied at necropsy with special reference to cardiac and renal lesions. Seven had myocardial fibrosis, which was attributable to scleroderma in four. Only two of the patients without other causes of heart failure and with myocardial fibrosis exhibited congestive heart failure. In one of these the heart failure was a prominent clinical feature, while in the other it appeared to contribute to the death caused primarily by carcinomatosis.

Renal lesions of significance were observed in three of the patients, each dying of uraemia. The renal lesions of scleroderma form a characteristic picture, with multiple arterial occlusions and cortical infarcts. Hypercellularity of glomeruli with fibrinoid necrosis of the basement membranes of the glomerular tuft is occasionally observed. The vascular lesions are impossible to distinguish from those of primary hypertension, but taken with the presence of multiple cortical infarcts and glomerular changes like those seen in lupus erythematosus they form a complex that appears to be specific for the kidney of scleroderma.—[*Authors' summary.*]

Renal Lesions in Scleroderma: Clinical and Pathological Features. TANGE, J. D. (1959). *Aust. Ann. Med.*, **8**, 27. 11 figs, 29 refs.

The author describes, from the Department of Pathology, University of Melbourne, the renal lesions in

three cases of scleroderma occurring in females aged 36, 46, and 69 years respectively. All three patients died of renal failure between 1 and 2 years from the onset of the disease. He has also collected and tabulated the relevant details of 34 similar cases reported in the literature.

The significant renal lesion is a mucoid and loose fibrous swelling of the walls of the intralobular arteries without inflammatory reaction, the arterial lumen being narrowed or obliterated. This interference with the blood flow leads to focal cortical infarcts. The appearances of the renal lesion and the clinical course of the disease are almost identical with those described in malignant hypertension. The administration of adrenal corticosteroids is not recommended in the treatment of scleroderma, since in a number of reported cases of this disorder these drugs have appeared to accelerate the progress of the hypertension or even to determine its appearance. *A. W. H. Foxell.*

Scleroderma of the Lungs. MILLER, R. D., FOWLER, W. S., and HELMHOLZ, F. H. (1959). *Proc. Mayo Clin.*, **34**, 66. 3 figs, 9 refs.

This paper records the results of a study at the Mayo Clinic of the pulmonary function of 22 (nine male and thirteen female) patients aged between 28 and 75 years with scleroderma. The first symptoms of the disease had occurred 4 months to 15 years (average 3·3) before this examination. The chief complaint referable to the lungs was exertional dyspnoea in fifteen cases and cough in three; in two patients there was also emphysema which, however, was probably unrelated. Radiography of the chest showed no significant amount of fibrosis in eight cases, slight localized fibrosis in two, moderate generalized fibrosis in two, and severe generalized fibrosis in ten; this was usually most prominent in the lower half or two-thirds of the lung fields. The severity of pulmonary fibrosis was not always proportional to the degree of sclerodermatous involvement of the skin.

Pulmonary function tests showed that total lung capacity was usually reduced in the presence of radiological fibrosis. Vital capacity was reduced in all the patients, with or without radiological signs, in no case exceeding 63 per cent. of normal. Residual volume was reduced only in those with severe pulmonary fibrosis. Arterial blood oxygen saturation was reduced in one of the patients with emphysema and in two with severe generalized fibrosis. Hypoxaemia after exercise occurred in most of the patients with generalized pulmonary fibrosis. *G. Loewi.*

Acrosclerosis: a Disease *sui generis* or a Variety of Diffuse Scleroderma. JABLÓNSKA, S., BUBNOW, B., and LUKASIAK, B. (1959). *Brit. J. Derm.*, **71**, 123. 36 refs.

Because of the conflicting views about the classification of acrosclerosis and its relation to diffuse scleroderma the authors, from the Warsaw Medical School, present an analysis of 45 cases of diffuse scleroderma, 33 of which were of acroscleroderma type. Of these 33 cases, only five were in men, and one of them was atypical. In all but three of the cases, there were simultaneous features of both so-called acrosclerosis and "diffuse" scleroderma, which made distinction between the two diseases impossible and led to the conclusion that acrosclerosis is a variety of diffuse scleroderma preceded or accompanied by Raynaud's phenomenon.

Sensory chronaxy is regarded as very important for prognosis, successive distinct and increasing prolongations being an indication of rapid development of the disease, whereas diminution is a favourable symptom. The pathogenesis of scleroderma is thought to be probably connected with damage to higher autonomic nervous centres, including those exerting vasomotor control. *E. W. Prosser Thomas.*

Treatment of Scleroderma. ZARAFONETIS, C. J. D. (1959). *Ann. intern. Med.*, **50**, 343. 9 figs, 10 refs.

The results of prolonged administration of potassium *para*-aminobenzoate in the treatment of 72 patients with scleroderma are reported in this paper from the Temple University Medical Center, Philadelphia. The drug was given in capsules or in a solution to a total daily dosage of 12 g. in adults and 1 g. per 10 lb. (4·5 kg.) body weight in children. There was marked improvement in 24 out of sixty patients treated for more than 3 months. The skin gradually became soft and freely movable over the subcutaneous structures. At the same time, the patient gained weight and began to experience a sense of well-being. In 34 patients the improvement was moderate, and in two "none to slight".

The author states that potassium *para*-aminobenzoate is less likely to give rise to anorexia or nausea than the crystalline acid or the sodium salt. Treatment is interrupted if anorexia or nausea supervenes, because hypoglycaemia may develop when the drug is taken during a period of inadequate food intake. The mode of action of *para*-aminobenzoate in scleroderma is not known, but it is suggested that the drug increases the amount of tissue oxygen. The activity of mono-amino oxidase is enhanced thereby and regression of fibrosis ensues.

In addition to administration of *para*-aminobenzoate, various forms of physiotherapy were found to be of value. For example, dynamic traction splints helped to minimize contractures of the fingers and deep-breathing exercises promoted expansion of the chest in cases of relative rigidity of the thoracic cage. Finally, "urecholine" was effective in patients complaining of dysphagia, a 5- or 10-mg. tablet being crushed and swallowed 30 minutes before meals. *A. Garland.*

Rheumatic Manifestations of Polymyositis and Dermatomyositis. PEARSON, C. M. (1959). *Arthr. and Rheum.*, **2**, 127. 5 figs, 12 refs.

Among seventeen cases of polymyositis and dermatomyositis seen in a 2½-year period at the Wadsworth Hospital, Veterans Administration Center, Los Angeles, there were eight in which various rheumatic and arthritic symptoms occurred. Certain features were found helpful in differentiating these eight cases from rheumatoid arthritis. Muscle weakness was prominent, particularly around the pelvic and shoulder girdles; the arthritis was

mild and did not produce either deformities or radiological changes; difficulty in swallowing was frequent; and the findings of increased serum transaminase activity and electromyographic changes were notable. However, the sheep cell agglutination test frequently gave positive results in these cases.

In most cases prolonged treatment with adrenal steroids produced significant relief from the rheumatic symptoms and improvement in muscular strength.

Oswald Savage.

Dermatomyositis and Malignancy: a Review of the Literature. WILLIAMS, R. C. (1959). *Ann. intern. Med.*, **50**, 1174. 1 fig., bibl.

Consideration of the So-called Collagen or Systemic Connective Tissue Diseases. [Review Article.] CRIEP, L. H. (1959). *Int. Arch. Allergy*, **14**, 27. 14 figs, bibl.

Malignant Scleroderma. Report of Five Cases. (Maligne Sklerodermie. Bericht uber fünf Fälle.) ŠŤÁVA, Z. (1959). *Dermatologica* (*Basel*), **118**, 371. 10 refs.

Visceral Manifestations of Progressive Scleroderma. (Viscerale manifestation der progressiven sklerodermie.) NÄGELE, E. (1959). *Klin. Wschr.*, **37**, 697. 9 figs, 48 refs.

Peripheral Vascular Changes in Certain Collagen Diseases: I. Photoplethysmographic, Oscillometric, and Capillaroscopic Observations in Rheumatoid Arthritis. (Sulle alterazioni dell'apparato vascolare periferico in alcune collagenosi. I. Rilievi fotopletismografici, oscillometrici e capillaroscopici nell'artrite reumatoide.) PANCALDO, A. (1959). *Rif. med.*, **73**, 691. 4 figs, 9 refs.

II. Photoplethysmographic, Oscillometric, and Capillaroscopic Observations in Scleroderma. (II: Rilievi fotopletismografici, oscillometrici e capillaroscopici nella malattia sclerodermica.) PANCALDO, A. (1959). *Rif. med.*, **73**, 901. 5 figs, 7 refs.

Diagnosis of Generalized Lupus Erythematosus. (Zur Diagnostik des generalisierten Lupus erythematodes.) KUHN, W. (1959). *Medizinische*, No. 29/30, 1385. 12 refs.

Treatment of Disseminated Lupus Erythematosus and Rheumatoid Arthritis with Methylprednisolone. MCMAHON, F. G., and GORDON, E. S. (1959). *J. Louisiana med. Soc.*, **111**, 201. 10 refs.

Disseminated Lupus Erythematosus as an Aetiological Factor in Cardiovascular Disease. (El lupus eritematoso diseminado (LED) como factor etiologico de affeccion cardiovascular.) MARCHENA, E. R., and HASBANI, J. (1959). *Rev. argent. Cardiol.*, **25**, 115. 8 figs, 96 refs.

Digestive Manifestations of the Collagen Diseases. (Manifestaciones digestivas de las enfermedades del colágeno.) ARCOS PÉREZ, M., and BARBIERI, M. (1959). *Rev. clin. esp.*, **73**, 116. 23 figs, 17 refs.

General Pathology

Comparative Studies of the Waaler-Rose Haemagglutination Reaction and the Latex-Fixation Test in Rheumatic Diseases. (Vergleichende Untersuchungen zwischen der Hämagglutinationsreaktion nach Waaler und Rose und dem Latexfixationstest bei rheumatischen Erkrankungen.) MÜLLER, W., and SCHUPP, E. (1959). *Z. Rheumaforsch.*, **18**, 97. 1 fig., 28 refs.

At the University Medical Clinic, Freiburg, the results of the latex fixation test and the Rose-Waaler haemagglutination reaction were compared in 257 patients with a variety of rheumatic disorders, in fifty patients with non-rheumatic diseases, and in thirty healthy subjects. The results of the two tests were generally in agreement, discordant results being most often due to a false positive reaction to the haemagglutination test. Neutralization of the rheumatoid factor with γ globulin produced a similar fall of titre in both tests. In progressive rheumatoid arthritis (68 cases) the latex fixation test gave 84·3 per cent. and the haemagglutination test 83·7 per cent. positive results. On the other hand in chronic polyarthritis with a cyclic course both tests usually gave a negative result, and this condition is therefore thought to represent a separate disease entity from rheumatoid arthritis. In the other rheumatic and non-rheumatic diseases positive results were very rare, and the group of healthy subjects gave entirely negative results. The latex-fixation test is preferred by the authors to the haemagglutination reaction as it is a simpler procedure, is more easily reproducible, and gives rise to fewer doubtful results. *G. W. Csonka.*

Latex-Fixation Test and the Agglutination Reaction with Sensitized Sheep Erythrocytes in the Demonstration of Characteristic Serum Changes in Rheumatoid Arthritis. (Der Latex-Test und die Agglutination mit sensibilisierten Schaf-Erythrozyten am Kältepräzipitat im Rahmen der für die primär-chronische Polyarthritis charakteristischen Serumveränderungen.) HARTER, F. (1959). *Z. Rheumaforsch.*, **18**, 150. 4 figs, 18 refs.

Serum from 256 patients (77 with rheumatoid arthritis, 105 with other rheumatic disorders, and 74 with non-rheumatic diseases) was examined by the latex-fixation test, the Rose-Waaler haemagglutination reaction, streptococcal L-agglutination and O-agglutination reactions, and the antistreptolysin reaction. The latex test has the merit of simplicity and gave positive results in 90 per cent. of cases of rheumatoid arthritis, which was a much higher proportion than was obtained with any of the other tests used. In the cases of other types of rheumatic disease and of non-rheumatic disease, the proportion of positive reactions was very low with all tests except the antistreptolysin reaction, which was positive in four (25 per cent.) of sixteen cases of atypical

chronic polyarthritis, in 22 (46 per cent.) of 48 cases of non-articular rheumatism, and in thirteen (17 per cent.) of the 74 cases of non-rheumatic disease, compared with sixteen (21 per cent.) of the 77 cases of rheumatoid arthritis. *G. W. Csonka.*

Differentiation between Rheumatoid Arthritis and Systemic Lupus Erythematosus by Sheep-cell Agglutination Tests. BLACK, A., GOLDIN, M., POSKE, R. M., and MALMED, L. (1959). *Arthr. and Rheum.*, **2**, 99. 10 refs.

In a combined study carried out at five centres in and near Chicago, an attempt was made to demonstrate clear-cut serological differences between rheumatoid arthritis (35 cases) and systemic lupus erythematosus (28 cases), and further to evaluate a group of seventeen cases of rheumatoid arthritis in which L.E. cells were present in the peripheral blood. Two variations of the sensitized sheep cell agglutination test were used. In the euglobulin method of Ziff the euglobulin fraction of the serum protein is separated by dialysis against an acid buffer at 4° C.; an initial dilution of 1 : 14 is tested and a titre of 1 : 28 is considered positive. In the cold precipitation method of Svartz the globulin is precipitated from the serum by adding fourteen volumes of cold distilled water and allowing it to stand for 48 hours at 4° C.; the initial dilution is 1 : 4 and a titre of 1 : 16 is considered positive.

The euglobulin test was highly sensitive for rheumatoid arthritis (71 per cent. positive), but the result was also positive in 54 per cent. of cases of systemic lupus erythematosus. The cold precipitation test, though less specific for rheumatoid arthritis, gave a positive result in only four cases (14 per cent.) of lupus erythematosus. In the patients with rheumatoid arthritis and L.E. cells both tests gave a higher proportion of positive results, and in higher titre, than in the group with rheumatoid arthritis and a negative L.E.-cell reaction. The authors suggest that both tests be performed when diagnostic problems involving these diseases arise.

Oswald Savage.

Histological, Histochemical, and Electron Microscopic Observations on Synovial Membrane. LEVER, J. D., and FORD, E. H. R. (1958). *Anat. Rec.*, **132**, 525. 9 figs, 19 refs.

Biopsy specimens of synovial membrane from joints of rabbits, cats, and man were examined histochemically and by light and electron microscopy at the Anatomy School of the University of Cambridge. While some parts of the synovium showed an absence of lining cells, in other situations these were several layers thick. The cytoplasm of the synovial cells, as well as the intercellular material, was deeply stained by the periodic-acid-Schiff method, and this reaction was not abolished by previous exposure to hyaluronidase. [Such abolition was not to be expected.] A metachromatic reaction was shown only by granules in a few deeply situated cells, assumed to be mast cells. Under the electron microscope the cells of the synovial surface were shown to contain dense, granular bodies 0·05 to 0·16 μ in diameter. Some of these cells had a degenerate appearance.

The authors consider that it is these surface cells and the cells immediately subjacent rather than the cells of the deeper layers or the mast cells which produce synovial mucin. The positive periodic-acid-Schiff reaction is presumed to be due to the hyaluric acid of the joint fluid. [The suggestion of Asboe-Hansen (*Ann. rheum. Dis.*, 1950, **9**, 149) that hyaluric acid is derived from mast-cell heparin is in any case most unlikely owing to the great chemical differences between these two acid polysaccharides.] *G. Loewi.*

Synovial Fluid Hyaluronate in Rheumatoid Arthritis. HAMERMAN, D., and SCHUSTER, H. (1958). *Arthr. and Rheum.*, **1**, 523. 13 refs.

The polysaccharide hyaluronate is the main cause of the viscosity of synovial fluid. This substance, a polymer of N-acetyl glucosamine and glucuronic acid, can be measured indirectly by determining the hexosamine content of synovial fluid or mucin clot. However, hexosamines also exist in combination with other synovial fluid proteins. The authors, working at the Albert Einstein College of Medicine, New York, have analysed nineteen specimens of synovial fluid from thirteen patients with rheumatoid arthritis and ten specimens from normal knees (eight of these being obtained *post mortem*), and determined the hyaluronate content by two independent methods:

(1) Precipitation of hyaluronate as a mucin clot by acetic acid, followed by determination of the hexosamine in the clot;
(2) By measuring the fall in hexosamine level in the fluid following hyaluronidase digestion and dialysis *in vitro*.

Control experiments showed that the hexosamine in mucin clot was derived solely from hyaluronate and that only hyaluronate hexosamine was rendered dialyzable by hyaluronidase.

The results of the two methods agreed. The hyaluronate hexosamine content of rheumatoid synovial fluid of greater than normal volume (measured by weight) averaged 0·4 mg. per g. and constituted 30 per cent. of the total fluid hexosamine content. In normal synovial fluids these values were 1·4 mg. per g. and 85 per cent. respectively. Rheumatoid and normal synovial fluids diluted to equal concentrations of hyaluronate hexosamine were shown to have similar viscosities (by the Ostwald method). It is suggested that dilution of hyaluronate, rather than depolymerization, seems to be the main cause of the low viscosity of synovial fluid in rheumatoid arthritis. *Allan St. J. Dixon.*

Laboratory Investigations in the Diagnosis of Rheumatic Diseases. GLYN, J. H., and IRVING, M. (1959). *Ann. phys. Med.*, **5**, 1. 26 refs.

A number of non-specific, "acute phase" serological tests indicative of inflammatory disease have in recent years been compared with the erythrocyte sedimentation rate (E.S.R.) and some of them recommended for clinical use. In this communication from the Prince of Wales and Edgware General Hospitals, London, the authors report the results of a clinical evaluation of some of

these tests, which they consider would be sufficiently simple for routine clinical use in separating significant from insignificant rheumatic disease. These included estimation of serum levels of C-reactive protein, total protein-bound polysaccharides, mucoprotein polysaccharides, total protein, and the serum protein : polysaccharide ratio, the results being compared with the E.S.R. as determined by the Westergren method. In all, a total of 455 tests were performed on 330 patients.

In 30 per cent. of 91 cases of active rheumatoid arthritis the E.S.R. was normal, whereas in only 3·5 per cent. of these cases were the results of the newer tests within normal limits. In one group of 73 cases in which the diagnosis was at first uncertain, but later became clear, 35 proved to be cases of rheumatoid arthritis; in this group the newer tests were found to be less reliable than the E.S.R.

The authors conclude as follows:

(1) In established rheumatoid arthritis and ankylosing spondylitis—conditions in which laboratory tests are not much needed—the newer tests give fewer false negative readings than the E.S.R.;

(2) As a measure of disease activity in cases not receiving drug treatment they are as accurate as the E.S.R.;

(3) As a help in solving diagnostic problems in rheumatic disease they are disappointingly unreliable.

The Winzler mucoprotein test was slightly more reliable than the others. As these tests are time-consuming they cannot justifiably be recommended.

Kenneth Stone.

Simple Precipitation Reaction for the Qualitative Study of the Rheumatoid Factor. (Eine einfache Pracipitationsreaktion zum qualitativen Nachweis des "Rheumafaktors".) MULLER, W. (1959). *Klin. Wschr.*, **37**, 86. 1 fig., 13 refs.

From the Medical Clinic of the University of Freiburg the author reports the evaluation of a quick and simple method of demonstrating the presence of rheumatoid factor in serum. The test is called the capillary precipitation test (C.P.T.). The antigen employed is a commercial solution of human γ globulin (16 per cent.) diluted with borate-saline buffer and heated at 63° C. for 30 minutes, a procedure which is believed to result in molecular aggregation. The patient's serum is not inactivated. Serum and γ-globulin solution are drawn up successively into a glass tube 8 cm. long and of about 5 mm. bore, care being taken to avoid the inclusion of an air-bubble between them. After 2 hours' incubation at 37° C. the tubes are refrigerated overnight and examined for precipitate at the point of contact of the two fluids. This test was carried out in parallel with the Rose-Waaler haemagglutination test, the latex fixation test of Singer and Plotz, and the author's "boundary layer reaction" (*Z. Rheumaforsch.*, 1958, **17**, 206). This last test is similar to the C.P.T., but is stated to be capable of providing a quantitative result; it employs heated γ globulin at 0·5 per cent. concentration and the patient's serum is diluted 1 : 6. Sera from 224 patients with various rheumatic disorders, 40 patients with non-rheumatic inflammatory disease, and 20 healthy subjects were examined.

In rather more than 75 per cent. of cases the result of the C.P.T. agreed with those of the other tests. In 16 per cent. of cases the result of the C.P.T. was negative when all 3 other tests gave a positive reaction, while very rarely the C.P.T. gave a positive result when the results of the other tests were negative—this usually occurred with the serum of patients who were probably not suffering from rheumatoid arthritis. The C.P.T. tended to give negative results in cases in which the titre of rheumatoid factor in the haemagglutination and latex fixation tests was low. Some correlation between the amount of precipitate formed and the titre of the latex fixation test was obtained when the γ-globulin concentration employed was 2·5 per cent.; with strengths of 5 per cent. or more, however, false positive results were obtained.

It is concluded that this test cannot at present replace the more elaborate reactions usually employed in testing for the rheumatoid factor. *G. Loewi.*

Electrophoretic Study of the Serum Factors Responsible for the Serological Reaction in Rheumatoid Arthritis, with Demonstration of Two Inhibitors. RANTZ, L. A., RANDALL, E., and KETTNER, D. (1959). *Arthr. and Rheum.*, **2**, 104. 18 refs.

In this study from the Stanford University School of Medicine, sera from healthy persons and from rheumatoid arthritics were separated into fractions by continuous flow electrophoresis on a paper curtain. Each fraction was used as the particle-coating substance in the latex-fixation test against a high titre rheumatoid serum. After the reactant had been discovered, a measurement of its concentration was made by determining the highest dilution which would give a definite reaction. Reactant was present in the gamma globulin fractions of all sera tested in fairly equal concentrations. The rheumatoid factor was a fast-moving gamma globulin. Fractions containing large amounts of rheumatoid factor, showed also a high concentration of reactant. Two inhibitors of the rheumatoid reaction were found in normal serum. The first inhibitor was present in the gamma globulin fractions and was probably reactant. The second inhibitor was more powerful than the first and was discovered in fractions containing alpha and beta globulins. It was absent from sera containing large amounts of rheumatoid factor. Further study of this second inhibitor may lead to improved methods for the diagnosis of rheumatoid arthritis if it can be shown to be present in diminished amounts in cases in which the rheumatoid factor itself cannot be demonstrated. *G. W. Csonka.*

Protein Patterns in Synovial Fluid and Serum in Rheumatoid Arthritis and Osteo-Arthritis. NETTELBLADT, E., and SUNDBLAD, L. (1959). *Arthr. and Rheum.*, **2**, 144. 22 refs, 8 tables.

In this study from the Söderssjukhuset, Stockholm, concentration of synovial fluid protein, acid glycoproteins, and sialic acid were estimated in 22 cases of rheumatoid arthritis and in seventeen cases of osteoarthritis. The electrophoretic protein patterns in serum

and synovial fluid were in close agreement in cases of rheumatoid arthritis, and this relationship was also found in osteo-arthritis, although the total protein content of synovial fluid was found to be much lower than that of serum. This may indicate that the type of permeability change in the synovial tissue is similar in both diseases. The sialic acid content of synovial fluid was closely related to the total protein content. Determinations of sialic acid did not help in the differentiation between fluids from cases of osteo-arthritis and rheumatoid arthritis. Acid glycoproteins are known to be increased in the serum of rheumatoid arthritics. This was confirmed and it was also found that the acid glycoproteins were abnormally high in the synovial fluid in rheumatoid arthritis. In osteo-arthritis the values were much lower in both serum and synovial fluid, and it is thought that this fact may be of value in differential diagnosis. The alpha$_2$ fraction of the synovial fluid decreased in both groups 2 to 4 days after intra-articular hydrocortisone acetate therapy. In rheumatoid arthritis, the alpha$_1$ and the beta fraction also decreased.

G. W. Csonka.

Comparative Distribution of Proteins and Glycoproteins of Serum and Synovial Fluid. DECKER, B., MCKENZIE, B. F., MCGUCKIN, W. F., and SLOCUMB, C. H. (1959). *Arthr. and Rheum.*, **2**, 162. 24 refs, 3 tables, 9 figs.

In this paper from the Mayo Clinic, the distribution of proteins and glycoproteins, determined by zone electrophoresis of the serum and synovial fluid in 71 patients with various rheumatic diseases and in ten patients without rheumatic disease, is compared. In cases of rheumatic disease there was a greater increase in globulins than in albumin, so that the distribution of proteins in synovial fluid approached the distribution of proteins in serum. Selective alteration in the alpha$_2$ glycoprotein of synovial fluid compared with the alpha$_2$ glycoprotein of serum was shown by the alpha$_2$ glycoprotein gradient:

$$\frac{\text{Percentage Concentration of alpha}_2\text{ Glycoprotein in Serum}}{\text{Percentage Concentration of alpha}_2\text{ Glycoprotein in Synovial Fluid}}$$

The value for the alpha$_2$ glycoprotein gradient was highest in patients without rheumatic disease and lowest in patients with synovitis and systemic rheumatic disease; the patients with synovitis not associated with systemic disease gave intermediate values. The reduction in the alpha$_2$ glycoprotein gradient in disease is thought to result from increased permeability of the synovial membrane. The alpha$_2$ glycoprotein gradient showed no change after the intra-articular injection of hydrocortisone acetate in three patients. *G. W. Csonka.*

Studies of Complement Fixation with Tissue Antigens in Rheumatic Subjects. (Untersuchung der Komplementbindung mit Gewebeantigenen bei Rheumakranken.) BAKOS, L., SCHULOF, Ö., SZILÁRD, J., and VAJDA, G. (1959). *Z. Rheumaforsch.*, **18**, 144. Bibl.

Extracts of heart, tonsil, lymph node, and granulomatous tissue obtained at biopsy or necropsy from persons with rheumatic disorders were prepared and exposed to ultrasonic radiation to reduce their anti-complementary effect and thus increase their activity as antigens. With these antigens a total of 599 complement-fixation tests (Wassermann technique) were performed on sera from patients with rheumatic diseases, from patients with non-rheumatic diseases, and from healthy subjects. The mean proportion of positive reactions with the four antigens was highest in the rheumatic group (45 per cent.) and lowest in the control group (14·7 per cent.).

Because of its lack of specificity this test is considered to be of little value for diagnostic purposes in rheumatology. It may, however, be useful in investigating problems of organ specificity. *G. W. Csonka.*

Effect of Histamine on the Polysaccharide System of Blood Serum. RICHTER, A. (1959). *Acta rheum. scand.*, **5**, 108. 26 refs.

Rheumatic Pneumonitis: Pathologic Features. SCOTT, R. F., THOMAS, W. A., and KISSANE, J. M. (1959). *J. pediat.*, **54**, 60. 8 figs, 15 refs.

Rheumatic Pneumonia. A Clinical, Radiological, and Pathological Study of Seven Cases. (La pneumopathie rhumatismale. Étude clinique, radiologique, et anatomo-pathologique à propos de sept cas personnels.) BRICHANT, J., MEERSSEMAN, F., DEHANT, J., and LAVENNE, F. (1959). *Acta clin. belg.*, **14**, 1. 20 figs, 40 refs.

Macroglobulins and Connective Tissue Disease. HEIMER, R. (1959). *Arthr. and Rheum.*, **2**, 266. 9 refs.

Rate of Hyaluronic Acid Production by Human Synovial Cells studied in Tissue Culture. CASTOR, C. W. (1959). *Arthr. and Rheum.*, **2**, 259. 2 figs, 12 refs.

Paper Electrophoresis of Serum Proteins in the Prognosis and Control of Treatment of Rheumatic Fever. (Znaczenie elektroforezy bibułowej białek surowicy w rokowaniu i kontroli leczenia choroby Bouillauda.) LEONOWICZ, K. (1959). *Pol. Arch. Med. wewnęt.*, **29**, 637-43. 12 refs.

Electrophoretic Studies of Synovial Fluid and Serum in Patients with Rheumatoid Arthritis treated with Hydrocortisone. (Badania elektroforetyczne płynów wysiękowych i surowicy chorych na gościec pierwotnie przewlekły po stosowaniu hydrokortyzonu.) HORST, A., and SOBOTA, S. (1959). *Pol. Arch. Med. wewnęt.*, **29**, 771. 7 refs.

Acid Mucopolysaccharide and 5-Hydroxytryptamine Content of Human Thrombocytes in Rheumatoid Arthritic and Non-arthritic Individuals. KERBY, G. P., and TAYLOR, S. M. (1959). *J. clin. Invest.*, **38**, 1059. 2 figs, 22 refs.

Clinical Value of Urinary Mucoprotein Estimation in Rheumatism. (Ocena wartości klinicznej oznaczania mukoproteidów w moczu chorych gośćcowych.) BUNSCH-WELKENS, K. (1959). *Pol. Arch. Med. wewnęt.*, **29**, 770. 30 refs.

Experience with the Waaler-Rose Test in Rheumatic Diseases. (Erfahrungemit dem Waaler-Rose Test bei rheumatischen Erkrankungen.) WÖLLNER, D., and FUCHS, W. (1959). *Dtsch. Arch. klin. Med.*, **205**, 611. 47 refs.

Study of Rheumatoid Arthritic Sera: Comparison of Spontaneous Precipitates and Gamma Globulin-Induced Precipitates. CHRISTIAN, C. L. (1959). *Arthr. and Rheum.*, **2**, 289. 8 figs, 13 refs.

Immunological Study of Rheumatoid Arthritis. Experimental Production of the Agglutination Activating Factor. (Étude immunologique de la polyarthrite chronique évolutive, sur la production experimentale du facteur activateur d'agglutination.) MATSUBARA, H., MAYEDA, A., TANABE, S., and SHICHIKAWA, K. (1959). *Ann. Inst. Pasteur Lille*, **97**, 218. 24 refs.

Serological Reactions in the Diagnosis of Rheumatoid Arthritis (Evaluation of Sheep Cell Test, F II Latex Particle Test, and F II Bentonite Flocculation Test). CECCHI, E., and FERRARIS, F. (1959). *Acta rheum. scand.*, **5**, 136. 16 refs.

Serological Diagnosis of Rheumatoid Arthritis. Comparison of a Simplified Test with the Latex-Agglutination Test. (Le diagnostic sérologique de la polyarthrite chronique évolutive. Comparaison d'un test simplifié avec le test d'agglutination au latex.) ORLOFF, S. (1959). *Brux.-méd.*, **39**, 1009. 8 refs.

Diagnostic Value of the Latex-Fixation Test in Rheumatoid Arthritis. (Der diagnostische Wert des Latex-Fixationstestes bei der rheumatischen Arthritis.) DAIKOS, G. K., KLONTZAS, E. I., and ATHANASIADOU, M. H. (1959). *Münch. med. Wschr.*, **101**, 1281. 19 refs.

Latex-Fixation Test of Synovial Fluid in Rheumatoid Arthritis. (Sul comportamento del test al lattice a goccia nel liquido sinoviale di malati affetti da artrite reumatoide.) EINAUDI, G., and GARELLI, R. (1959). *Reumatismo*, **11**, 148. 18 refs.

Pathogenetic Problems concerning the Rheumatoid Factor. (Problemi pathogenetici relativi al fattore reumatoide.) BONOMO, L. (1959). *Reumatismo*, **11**, 159. 2 figs, 54 refs.

Research into the Presence of the Rheumatoid Factor in Homogenates of the Articular Capsule and in Blister Fluid. (Ricerche sulla presenza del fattore reumatoide nell'omogenato di capsula articolare e nel liquido di bollo.) EINAUDI, G., GARELLI, R., and MARRAZZI, G. (1959). *Reumatismo*, **11**, 156. 2 refs.

Relationship between a Serum and Tissue Inhibitor and the Rheumatoid Disease Agglutinating Factor. GRAY, J. D. (1959). *J. Immunol.*, **83**, 1. 10 refs.

Chromatographic Studies of the Rheumatoid Factor. LOSPALLUTO, J., and ZIFF, M. (1959). *J. exp. Med.*, **110**, 169. 13 figs, 25 refs.

Separation of Factors in Lupus Erythematosus Serum reacting with Components of Cell Nuclei. GOODMAN, H. C., FAHEY, J. L., MALMGREN, R. A., and BRECHER, G. (1959). *Lancet*, **2**, 382. 1 fig., 17 refs.

Problem of the Specificity of the Lupus Erythematosus Phenomenon. (Zur Frage der Spezifität des Lupus-erythematodes-Phänomens.) BEICKERT, A., and GEIDEL, H. (1959). *Ärzt. Wschr.*, **14**, 561. 7 figs, 28 refs.

Circulating Anticoagulants in Disseminated Lupus Erythematosus. MEDAL, L. S., and LISKER, R. (1959). *Brit. J. Haemat.*, **5**, 284. 1 fig., 23 refs.

Serum α-Glycoproteins in Rheumatic Fever. Effects of Salicylate Therapy. (Le α-glicoproteine nella malattia di Bouillaud. Effetti del trattamento salicilico.) GIULIANO, G., MARINONI, G. F., and RIZZA, O. (1959). *Progr. med.* (*Napoli*), **15**, 305. 10 refs.

Fibrinogen Polymerization Test in Various Diseases of Childhood with Particular Reference to Rheumatic Fever. (Il test della polimerizzazione del fibrinogeno in varie malattie infantili con particolare riguardo alla malattia reumatica.) MAZZEO, G. (1959). *Lattante*, **30**, 405. 1 fig.

Lesions of Auricular Appendages in Rheumatic Heart Disease. I. Normal Histology of Auricular Appendages. II. Rheumatic Lesions of the Left Auricular Appendage. LI-LI, L., PAO-MEI, W., and SHOU-YEN, K. (1959). *China med. J.*, **79**, 1; 7. 6 figs, 7 refs.; 12 figs, 6 refs.

ACTH, Cortisone, and Other Steroids

Inhibitory Effect of Triamcinolone on Adrenal Function. HATFIELD, C. B., and SHUSTER, S. (1959). *J. clin. Path.*, **12**, 140. 1 fig., 11 refs.

Inhibition of the secretion of hydrocortisone, which is normally caused by injection of certain steroid hormones, has proved a useful means of demonstrating an intact pituitary-adrenal axis, and in some cases helps to distinguish between adrenal cortical neoplasia and hyperplasia. A disadvantage of the technique is that many of the steroids, when given in suppressive doses, contribute significantly to the metabolites, the levels of which in the urine and plasma are used as an index of adrenal activity.

In this paper from the Postgraduate Medical School of London a study is reported of the ability of triamcinolone to depress the secretion of hydrocortisone by the adrenal cortex in a healthy male aged 31 years, and a girl aged 16 years, with cirrhosis of the liver without ascites. The urinary excretion of corticosteroids and the plasma hydrocortisone level were estimated for a control period of 2 days. The subjects were then given 8 mg. triamcinolone four times a day for 5 and 11 days respectively, and the urinary excretion of steroids and the plasma hydrocortisone level again determined at intervals. Triamcinolone caused marked depression of hydrocortisone secretion and did not produce a significant amount of plasma or urinary chromogen. ACTH (corticotrophin) gel given while the subjects were still receiving triamcinolone immediately restored hydrocortisone secretion, indicating that the drug did not act directly on the adrenal cortex. Toxic effects of the steroid necessitated cessation of the trial in one additional subject. *P. A. Nasmyth.*

Adrenocortical Function in Obesity. (Les fonctions cortico-surrénales dans l'obésité.) ALBEAUX-FERNET, M., CHABOT, J., and ROMANI, J. D. (1959). *Sem. Hôp. Paris*, **35**, 993. 1 fig., 28 refs.

This paper from the Hôpital Laënnec and the Institut National d'Hygiène, Paris, describes a study of adrenocortical function in 53 women with obesity, none of whom was manifestly suffering from Cushing's disease. In most cases the excretion of 17-ketosteroids, like that of 17-hydroxysteroids, was abnormally low or at the lower limit of normal, though low readings for 17-hydroxysteroids occurred more constantly than low readings for 17-ketosteroids. This partial adrenal insufficiency was considered to be purely functional, due to confinement to bed and restrictions of hospital life.

The excretion of aldosterone was studied in five cases while the subjects were given successively a normal sodium intake, a moderately low-sodium diet, and a high-sodium diet. In two cases the subjects were then given a very low sodium intake (200 mg. daily) and in one a high sodium intake (6 g. daily). The amount of aldosterone excreted and its variation with the amount of sodium in the diet were within normal limits. It is concluded that the amount of extracellular fluid in the obese is normal and that the excess fluid and sodium in such cases are held in the interstitial spaces. In the obese subject given a high sodium intake the excess was not eliminated so that there was a marked rise in weight although in other respects the diet remained restricted. In this sense obesity is comparable to oedema with salt retention. In two cases the excretion of aldosterone was studied at different points in the menstrual cycle. There was frank hyperaldosteronism during the second half of the cycle, comparable with the hyperaldosteronism that has been observed in obese women during periods of gain in weight. *A. G. Mullins.*

Adrenal Cortex in Itsenko-Cushing's Disease. [In Russian.] TARAKANOV, E. I., and ŠČITKOVA, T. A. (1959). *Probl. Endokr. Hormonoter*, **5**, 58. 24 refs.

The authors have studied the morphological and histochemical changes in the cells of the adrenal cortex in four cases of Cushing's disease. Three of the specimens were taken from glands totally or partially resected at operation and one from a patient who died of pneumonia in a late stage of the disease.

The hypertrophy and hyperplasia of the adrenal cortex found in this disease are due to the excessive production of corticotrophin by the pituitary gland as a result of the poor output of hydrocortisone. The effect of this is to produce an intensive synthesis and secretion of androgens such as 4-androsterone, androstenedione, and 11-hydroxyandrostenedione. Two stages of hypertrophy were observed:

(1) Accumulation of lipids in the cells (initially in the zona glomerulosa) and increased secretion of corticosteroids, particularly of glucocorticoids;

(2) Reduction of lipids and perverted biosynthesis of steroid hormones, with increase in the neutral 17-ketosteroids and decrease in oestrogens.

The two stages are characterized by corresponding histochemical changes.

The authors advocate large doses of cortisone or hydrocortisone in the treatment of the disease to suppress the reaction of the pituitary and the consequent excessive production of virilizing and neutral steroids. They consider that resection of the adrenal glands is justifiable only in the first stage of cortical hypertrophy. The article is illustrated by five photomicrographs reproduced in colour. *L. Firman-Edwards.*

Clinical and Metabolic Study of a New Corticosteroid, Dexamethasone. (Étude clinique et métabolique d'un nouveau corticostéroïde, la dexaméthasone.) ROUSSO, C., and PERRIER, C. V. (1959). *Schweiz. med. Wschr.*, **89**, 405. 3 figs, 10 refs.

From the University of Geneva the authors report the clinical and metabolic effects of dexamethasone (9α-fluoro-16α-methyl prednisolone), a recently introduced corticosteroid. It was found that dexamethasone was six to eight times more active than prednisolone and did not give rise to sodium or water retention. One case of heart failure is described in which a water diuresis was obtained with dexamethasone. Care, however, must be taken in its use for diabetics, since impaired carbohydrate tolerance results.

Dexamethasone is considered by the authors to be the most effective suppressive of ACTH (corticotrophin) by

its action on the anterior pituitary. They found that a single oral dose of 1·0 mg. could reduce the plasma 17-hydroxycorticoid level to zero within 8 hours. No serious side-effects were noted, except in one patient, a young man aged 21, who developed severe melaena due to ulceration of the colon while receiving a dosage of 10 mg. dexamethasone daily. Caution is therefore urged in the use of this steroid. *I. McLean Baird.*

Dexamethasone in the Treatment of 100 Patients. Comparison with Prednisone and 6-Methylprednisolone. (100 malades traités par la dexaméthasone. Comparaison avec la prednisone et la 6-méthyl-prednisolone.) LICHTWITZ, A., HIOCO, D., and GRESLÉ, C. (1959). *Sem. Hôp. Paris*, **35**, 1570. 9 figs, 24 refs.

The authors describe the various attempts that have been made to modify the corticoids, especially prednisolone, so as to remove their anti-inflammatory action. These have included halogenation (substituting fluor in the C_9 position), deshydrogenation (between C_1 and C_2), methylation (in various positions, with resulting different effect on sodium retention and anti-inflammatory action), and hydroxylation—the addition of an OH group in C_{16} causes reduction or disappearance of sodium retention.

At the Hôpital Saint-Anne, Paris, one of these compounds, 6α-methyl-prednisolone (6-MP), was tried on 61 patients with rheumatoid arthritis or other arthroses; it seemed to produce improvement similar to that obtained with prednisone, but not always in the same patients, nor were the side-effects of 6-MP always of the same order as those caused by prednisone. The second compound tried was 16α-methyl-9α-fluoroprednisolone (dexamethasone) and this was given to 100 patients, of whom 52 had osteo-articular affections, 29 had allergic conditions, eleven had endocrine disorders (five had Addison's disease, four hypopituitarism, and two the adrenogenital syndrome), and eight had varied disorders, including colitis, hypoglycaemia, cirrhosis, and pleural carcinomatosis. Most of the patients were adults aged over 45 and the daily dosage of dexamethasone varied from 0·2 to 4 mg.

For the patients with osteo-articular disease, treatment was continued for up to 9 months, the average dose of dexamethasone being between 1 mg. and 3 mg. daily. It was shown that the ratio of effective action of prednisolone to dexamethasone and of 6-MP to dexamethasone was between 5 and 7 (that is, dexamethasone proved to be five to seven times more effective). In the patients with respiratory and skin allergy, doses not exceeding 1·5 mg. daily controlled the condition effectively. In the five cases of adrenal insufficiency, dexamethasone was found to be ten times more active than prednisone, and in the two cases of the adrenogenital syndrome over forty times more active. *V. C. Medvei.*

Intolerance, Complications, and Accidents Caused by Dexamethasone (16 M.F.P.). (Intolérances, incidents et accidents provoqués par la dexaméthasone (16 M.F.P.).) LICHTWITZ, A., HIOCO, D., and GRESLÉ, C. (1959). *Sem. Hôp. Paris*, **35**, 1581. 8 figs, 24 refs.

Among the 100 patients treated with dexamethasone described above (see previous Abstract) the undesirable side-effects observed were studied in the following groups:

(1) Tissue effects, including rounding of the face, slight Cushing appearance, hirsutism, acne, increase in weight, purple striae, and skin infection.

(2) Psychological effects, such as euphoria, irritability, insomnia, hypomania, headaches, paraesthesiae, and giddiness.

(3) Visceral conditions, including effects on the heart (dyspnoea, precordial pain, palpitations, hypertension), effects on the blood vessels (purpura), effects on the digestive tract (increased appetite, sensation of taste, excessive thirst, nausea, postprandial pain, meteorism, or gastric haemorrhage), and decalcification of bone.

(4) Metabolic effects, particularly those on the sodium, potassium, water, calcium, and phosphorus levels.

(5) Effects on the metabolism of proteins and carbohydrates, including the production of hyperglycaemia, particularly in diabetic patients.

(6) Glandular effects—of which, however, none was observed.

The authors' general conclusions are that the side-effects of dexamethasone and 6-methyl-prednisolone are not only rarer and much less marked than, but also qualitatively different from, the comparable side-effects of prednisolone, prednisone, and other corticoids. Effects on the heart appear to be completely absent, and digestive disturbances were also rarer, although no final conclusion could be reached as regards gastric haemorrhage, since the number of patients was small. The metabolic effects were similar to those of prednisone. The powerful anti-ACTH action of the drug did not seem to cause adrenal insufficiency. They therefore conclude that these two new corticoids, and especially dexamethasone, are far superior in their action to prednisone, prednisolone, and other earlier forms, and also have a considerably wider margin of safety. *V. C. Medvei.*

Combined Treatment with Antibiotics and Corticosteroids. [In Russian.] KASSIRSKIJ, I. A., and IVANOV, K. P. (1959). *Ter. Arh.*, **31**, 13.

A study of the literature concerning the use of corticosteroids in acute infections reveals a conflict of opinion, some authors holding that they diminish the resistance of the infected organism and reduce the antimicrobic activity of antibiotics, while others assert that there is a synergic effect, the hormones reducing reactivity and inflammatory processes while the antibiotics suppress the infection.

The present authors conclude from their own experience that for the treatment of certain infective processes, particularly those in which allergic phenomena predominate (such as tuberculous pleurisy), and of protracted severe sepsis (such as osteomyelitis) the combination of steroids and antibiotics is superior to the use of antibiotics alone. Indeed, several cases are cited in which complete control was not attained until antibiotic treatment was supplemented with cortisone or corticotrophin (ACTH). Two illustrative cases of infective

endocarditis, two of osteomyelitis, and one of cholangitis with general sepsis are described in full.

L. Firman-Edwards.

Adrenal Hormones in Rheumatology. (Zastosowanie hormonów nadnercza w reumatologii.) SABOTA, S. (1959). *Pol. Arch. Med. wewnęt.*, **29**, 655. 4 figs, 9 refs.

Consequences of Prolonged Courses of Corticotherapy. (Les conséquences de la corticothérapie en cures prolongées.) LOUYOT, P., GAUCHER, A., and MATHIEU, J. (1959). *Rev. Rhum.*, **26**, 332. 8 figs.

Undesirable Side-Effects of Dexamethasone with Special Reference to Prolonged Treatment. (Sugli effetti secondari sfavorevoli del desametasone con particolare riguardo alle cure protratte.) ROBECCHI, A., DI VITTORIO, S., and EINAUDI, G. (1959). *Reumatismo*, **11**, 117. 23 refs.

Observations on Carbohydrate Metabolism during Dexamethasone Therapy. (Rilievi e considerazioni sul comportamento del metabolismo glicidico in corso di terapia con desametasone.) EINAUDI, G., and GHINAMO, G. (1959). *Reumatismo*, **11**, 140. 19 refs.

Steroid Therapy in Rheumatoid Diseases. LOCKIE, J. M. (1959). *J. Amer. med. Ass.*, **170**, 1063. 3 refs.

Joint Infections following Steroid Therapy: Roentgen Manifestations. TONDREAU, R. L., HODES, P. J., and SCHMIDT, E. R. (1959). *Amer. J. Roentgenol.*, **82**, 258. 5 figs, 15 refs.

Other General Subjects

Response to Serotonin and Its Antagonists in Patients with Rheumatoid Arthritis and Related Diseases. SCHERBEL, A. L., and HARRISON, J. W. (1959). *Angiology*, **10**, 29. 2 figs, 8 refs.

At the Cleveland Clinic Foundation, Ohio, the local response to injection of serotonin in 23 patients with rheumatoid arthritis was compared with that in sixteen healthy controls. In the patients only uninvolved joints were injected. The dosages of serotonin were 0·01 mg. intra-articularly into the proximal interphalangeal joints of the fingers, 0·05 or 0·1 mg. periarticularly near a proximal finger joint, and 0·1 mg. intradermally on the back of the hand. Diffuse painful oedema and erythema with cyanosis, sometimes spreading over the back of the hand and the wrist and lasting 1 to 2 hours or more, developed in twenty of the patients but in only one of the controls. Antagonists to serotonin given intravenously abolished the cyanosis in 10 minutes. Similar results were obtained in fifteen patients with systemic lupus erythematosus or scleroderma. It is concluded that patients with rheumatoid arthritis and related disorders are less able to inhibit serotonin than are healthy subjects. *J. A. Cosh.*

Hydrarthrosis resulting from Oedema and Vascular Disorders of the Lower Limbs. (Les hydrarthroses au cours des oèdemes et des troubles vasculaires des membres inférieurs.) LIÉVRE, J.-A., and BERTHAULT, J.-M. (1959). *Rev. Rhum.*, **26**, 313. 11 refs.

Polymyositis (A Clinical and Electromyographic Study). (Le polimiositi (Studio clinico ed elettromiografico).) DE CARLO, M., GAY, A., CASERTANO, F., and GATTO, E. (1959). *Arch. E. Maragliano Pat. Clin.*, **15**, 717. 9 figs, 50 refs.

Raynaud's Phenomenon in Rheumatology. (El fenomeno de Raynaud en reumatologia.) SILVA L., C., and ZELDIS, A. (1959). *Rev. argent. Reum.*, **24**, 123.

Tietze's Syndrome associated with Paroxysmal Recurrent Tachycardia. JACOBS, J. E., and CONNERS, J. J. (1959). *Sth. med. J. (Bgham, Ala.)*, **52**, 774. 5 figs, 6 refs.

Measurement of Hip Motion in the Sagittal and Coronal Planes. MILCH, H. (1959). *J. Bone Jt Surg.*, **41A**, 731. 8 figs, 5 refs.

Medico-legal Incidence of Forms of Lumbago of Traumatic Origin. (Incidence médico-légales des lumbagos traumatiques.) SICHÈRE, R. M., CHEVALLIER, J., and VAN PETEGHEM, J. (1959). *Rev. Rhum.*, **26**, 275. 7 refs.

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INDEX TO VOLUME XVIII, 1959

* indicates that only the title of the article is given

ABELSON, D., 143
Acid, acetylsalicylic, and fever of Still's disease, 296
——, butanol acetic, 314
——, homogentisic, in differential diagnosis, 51
——, indolyl acetic, 314
——, —— lactic, 314
—— mucopolysaccharides of connective tissue, 5
——, nicotinic, ester of (Trafuril), effect of aspirin on cutaneous response to, 137
—— polysaccharide, urinary excretion of, in arthritis, rheumatoid, 239
——, 4-hydroxy-isophthalic (HIPA), in arthritis, rheumatoid, 190
Acqui Prizes, 1959, awards, 264
ACTH in arthritis, rheumatoid, 100
—— therapy compared with pituitary tissue implantation, 35
Acute rheumatism: *see* Rheumatism, acute
——: *see also* Steroid
Adrenal cortex, salicylates and, 298
Adrenalectomy in rats, 309
Agammaglobulinaemia in differential diagnosis, 51
—— and joint disease, 4
Agglutination tests, 3, 24, 26, 217, 307
—— —— in assessment of arthritis, 279
—— —— with British latex suspension, 301
—— ——, differential, in arthritis, juvenile, 225
—— ——, ——, ——, ——, compared with adults, 233
—— —— for rheumatoid factor, 322
ALEXANDER, W. R. M., 58, 261
——: *see* Bremner, J. M., etc., 279
Aminopyrine therapy, 25
Amyloidosis, 2
——, Congo red resorption in, 10
Analgesics compared with prednisolone in arthritis, rheumatoid, 173
Anasarca and polyserositis, Congo red resorption in, 10
Ankylosing spondylitis : *see* Spondylitis, ankylosing
ANSELL, B. M., 330, 331
Anti-inflammatory compounds, 66
Antinuclear factor in disseminated lupus erythematosus, 261
Antistreptolysin in prognosis of arthritis, rheumatoid, 24, 26
Anxiety as factor in arthritis, rheumatoid, 2
Argentine League against Rheumatism, 148
ARONOFF, A., 263
Arteritis, temporal or giant cell, 56
Arthritis, acute infections in, 50
——, gouty, diagnosis of, 50
——, pituitary tissue injection in, 34
—— in Reiter's disease, 38
——, rheumatoid, ACTH in, 100
——, ——, in adults and juveniles, compared, 233
——, ——, aspirin and cutaneous response of nicotinic acid (Trafuril) in, 37
——, ——, complicated by pericarditis, L.E. cells, and tubercular lung nodules, 57
Arthritis, rheumatoid, controlled trial of phenylbutazone derivative (G27 202) in, 244
——, ——, cortisone analogue trials in, 120
——, ——, dermal avidity for Congo red in, 8
——, ——, epidemiology of, in Liberia, 305
——, ——, familial incidence of, 279
——, ——, functional capacity in, 95
——, ——, gamma globulin in, 319
——, ——, hypersensitivity in, 1
——, ——, irritants in synovial fluid in, 69
——, ——, juvenile, differential agglutination test in, 225
——, ——, ——, —— —— ——, compared with adults, 233
——, ——, latex suspension in agglutination tests for, 301
——, ——, marrow iron in, 57
——, ——, pleural effusion in, 56
——, ——, prednisolone compared with aspirin or other analgesics in, 173
——, ——, prognosis of, serological laboratory tests for, 24
——, ——, pyrazoles and steroids in, 259
——, ——, sanatorium treatment for, 91
——, ——, statistical method of testing therapy, 189, 202
——, ——, urinary excretion of acid polysaccharide in, 239
——, ——, —— indoles and other "Ehrlich's reagent reactors" in, 313
——, ——, vital capacity in, 70
——, surgery in, 29
—— with uveitis and genital infection, 145
Arthroplasty of wrist and hand, 31
Aspirin and other analgesics compared with prednisolone, 173
—— in arthritis, rheumatoid, 190, 195
——/cortisone trials in arthritis, rheumatoid, 120
—— and cutaneous response to ester of nicotinic acid (Trafuril) in arthritics, 137
Assessment of arthritis in controlled therapeutic trial, 245
—— of arthritis, familial, 279
Atrophy, limb, in rabbit, connective tissue metabolism and, 129
Australian Rheumatism Association, 144
—— —— Council, 144

BADLEY, B. W. D., 330
BAKOS, L.: *see* Forgács, P., etc., 34
BALL, J., 63
BALLANTYNE, R. D., 69
BARFORD, L. J., 57, 261
Barium meals in arthritis, rheumatoid, 186
BARTOŠ, J.: *see* LENOCH, F., etc., 45
*BAUWENS, P., 264
BENCE-JONES protein in differential diagnosis, 51
Bentonite flocculation test, 58

*Bergin, J. D., 70
Bile duct ligation and experimental inflammation, 310
Biochemistry of sulphated substances, 61
Biopsy in Tietze's syndrome, 249
Black Notley experiment, 91
*Bland, J. H., 259
Blécourt, J. J. de, 260
Blood loss, faecal, and salicylate therapy, 62
—— pressure changes in arthritis, rheumatoid, 184
—— studies, 143
—— ——: *see also* Agglutination tests
Boerma, F. Westendorp: *see* Otten, H. A., etc., 24
Boies, L. R., Jr.: *see* Malawista, S. E., etc., 305
Bone disease, metabolic, simulating rheumatic disorders, 63
Book Reviews:
Rotes Querol, J.: Manifestaciones osteoarticulares de la Brucelosis (1959), 264
Sèze, S. de, Ryckewaert, A., and Maître, M.: L'épaule en pratique rhumatologique (1959), 329
Soila, Pekka: Roentgen Manifestations of Rheumatoid Arthritis (1958), 68
Brain, R., 142
Bremner, J. M., Alexander, W. R. M., and Duthie, J. J. R.: Familial incidence of rheumatoid arthritis, 279
British Association of Physical Medicine, 259, 264
British Medical Association Annual Meeting, 1959, Rheumatic Diseases, 148
British Rheumatic Association, Officers, 1959, 149
Brooke, J. W., and Slack, H. B.: Metabolism of connective tissue in limb atrophy in the rabbit, 129
Brown, A. Rowatt, 69
Buchan, J. F., 58
Bywaters, E. G. L.: Heberden Round, 1959, 330, 331 *ter*
—— 60, 65, 98, 146, 147, 262, 263
——, Carter, M. E., and Scott, F. E. T.: Differential agglutination titre (D.A.T.) in juvenile rheumatoid arthritis, 225
——, ——, ——: Comparison of differential agglutination titre in juvenile and adult rheumatoid arthritis, 233
——: *see* McMinn, F. J., etc., 293
——: *see* Parkins, R. A., etc., 8

Canadian Rheumatism Association, 148, 329
Cardoe, N.: Controlled trial of G27 202 (p-hydroxyphenylbutazone) in rheumatoid arthritis, 244
*Carpal tunnel syndrome, 70
Carter, M. E., 65
——: *see* Bywaters, E. G. L., etc., 225, 233
Cartilage, articular, in lupus erythematosus, systemic, 112
Catterall, R. D., 145
*Chandler, G. W., 55
Chapman, L.: *see* Savage, O., etc., 100
*Charnley, J., 259
Childhood deprivation as factor in arthritis, 69
Children, arthritis, rheumatoid, in, 225, 233
Chloroquine in arthritis, rheumatoid, 58
Christie, H. K., 69
Chromatography in diagnosis of arthritis, rheumatoid, 313
Coke, H.: Experience with British latex suspension for agglutination tests in rheumatoid arthritis, 301
Collagen analysis in limb atrophy, 130
—— diseases, gamma globulin levels in, 318
Collins, D. H., 143
Coltart, W. D., 143
Congo red, intracutaneous, resorption of, 8
Conjunctivitis in Reiter's disease, 38
Connective tissue components in study of arthritis, 5
—— ——, immuno-histological study of, 207
—— —— metabolism in limb atrophy in rabbit, 129
—— ——, nucleo protein-latex agglutination test in disorders of, 255
—— —— studies, 142
Cooksey, F. S., 261
*Coomes, E. N., 264
Copeman, W. S. C., 146
——: *see* Savage, O., etc., 100
Corticotrophin: *see* ACTH
Cortisone acetate and experimental inflammation, 310
—— analogues, trials of, in arthritis, rheumatoid, 120
——, intra-articular, in osteo-arthritis of the knees, 325
—— in iritis, "rheumatic", 46
——: *see also* Steroid
Cregan, J. C. F.: Indications for surgical intervention in rheumatoid arthritis of the wrist and hand, 29
*——, 259, 264, 330
Criteria for assessing patients, clinical progress, 176
*Cronin, E. J., 70
Cruickshank, B.: Lesions of joints and tendon sheaths in systemic lupus erythematosus, 111
Csaszar, G.: *see* Forgács, P., etc., 34
Csonka, G. W.: *see* Oates, J. K., etc., 37
Currie, J. P., 66

Davis, P. S.: *see* Savage, O., etc., 100
Dermatomyositis, diagnosis of, 50
Dexamethasone, 59, 126
Diagnosis of arthritis, rheumatoid, criteria for, 50
—— ——, ——, in population survey, 306
Disease activity in arthritis, rheumatoid, 95, 96
—— —— in juvenile arthritis and D.A.T., 228
Disk, vertebral, radiology of, in spondylitis, 17, 18
Dixon, A. St. J., 62, 146, 147, 262, 330, 331
Dollery, C. T., 331
Drugs, studies of, 143
Duncan, H., 000
"Durafoam" in splint making, 261
Duthie, J. J. R., 60, 97, 147, 261
——: *see* Bremner, J. M., etc., 279
——: *see* Truelove, L. H., etc., 137

Effusion, pleural, in arthritis, rheumatoid, 56
Ehrlich's reagent reactors in arthritis, rheumatoid, 313
Eisen, V., 143
Electrophoresis, 318
Ellis, H. A., and Felix-Davies, D.: Serum complement, rheumatoid factor, and other serum proteins in rheumatoid disease and systemic lupus erythematosus, 215
Empire Rheumatism Council, 22nd Annual Report, 142
Engerman, R. L., and Meyer, R. K.: Anti-inflammatory effect of obstructive jaundice in rats, 309
Epidemiology of acute rheumatism in young men, 285
——, evaluation of a method for, 305
—— of rheumatic disease, 66
Erythema nodosum, 51
Erythrocyte sedimentation rate, ACTH therapy and, 103
—— —— —— in cortisone analogue trials, 122
—— —— —— in diagnosis of arthritis, 50, 282
—— —— —— and sanatorium treatment, 95
Eye involvement in Reiter's disease, 38

Factor, rheumatoid, serological estimation of, 186
Family of arthritis patients, 280
FEARNLEY, G. R., 60, 330
*FEARNLEY, M. E., 264
Fellowships, Empire Rheumatism Council, 142
Female, Reiter's disease in, 37
——, spondylitis, ankylosing, in, 15
FESSEL, W. J.: Nucleoprotein-latex agglutination test in connective tissue diseases, 255
Fever patterns of Still's disease and acute rheumatism, 293
——, rheumatic: *see* Rheumatism, acute
Fibroblasts and arthritis, 6
Fingers, surgery of, in arthritis, 30
FLADEE, H. W., NEWNS, G. R., SMITH, W. D., and WEST, H. F.: Trials of cortisone analogues in the treatment of arthritis, rheumatoid, 120
Fluid retention, 108
Fluorescence in photo-micrography of connective tissue, 210
FORGÁCS, P., BAKOS, L., CSASZAR, G., and RIESZ, E.: Effect of intramuscular injection of pituitary tissue in rheumatoid arthritis, 34
FOURMAN, P., 142
Fractures in Still's disease, 330
FRANÇON, F., 263
FRENCH, P., 143
Functional capacity on arthritis, rheumatoid, 95, 96, 236
F.II agglutination tests in diagnosis of arthritis, rheumatoid, 306
—— sensitizing agent in agglutination tests, 302

Gamma globulin levels in collagen diseases, 318
—— —— in serology of rheumatoid disease, 217
*GARLICK, C., 70
Genital infection in Reiter's disease, 38
GILLILAND, I. C., 143
Glycosuria and ACTH, 108
GLYN, J. H., 330
*GODFREY, C. M., 264
Gold therapy, 25
GOOD, M. S., 55 *bis**, 56
Gout, kidney in, 146
——, misdiagnosis of, 145
Granuloma tissue in experimental inflammation, 310
*GRAY, F. D., 259
GREENBAUM, D., 146
GREENBURY, C. L., 57
*GREENWOOD, R., 264
GRESSON, C., 69
Grip strength in assessment of arthritis, rheumatoid, 101, 102, 122, 191
G27 202: *see* Phenylbutazone

Haemoglobin level in diagnosis of arthritis, 282
—— percentage and sanatorium treatment, 95
HAJNAL, J., SHARP, J., and POPERT, A. J.: A method for testing analgesics in rheumatoid arthritis using a sequential procedure, 189
*HALL, G. F., 70
Hand, rheumatoid, tendon lesions in, 147
——, surgery of, in arthritis, 29
HARRIS, R., *259, 261 *bis*, *264
HART, F. DUDLEY, 59
—— and ROBINSON, K. C.: Ankylosing spondylitis in women, 15
HARTFALL, S. J., *55 *bis*, 263
HEALD, C. B., 261
Heart involvement in rheumatism, acute, 288
Heberden Oration, 1958, 1
Heberden Round, 1959, 330
HEBERDEN SOCIETY:
Annual Report, 1958, 54
Officers for 1959, 55
Clinical Meetings,
October 11, 1958, 55
December 5 and 6, 1958, 61
February, 1959, 145
October, 1959, 330
Joint meeting with British Association of Physical Medicine, Buxton, July, 1959, 259
Heel lesions in Reiter's disease, 38
Heredity in gamma globulin types and arthritis, 318
HESS, E., 143
HICKLIN, J. A., 143
HIGHTON, T. C., 69
HILL, A. G. S., *55, 57, 330, 331
Histology of connective tissue, 207
—— in diagnosis, 50
—— of lupus erythematosus, systemic, 112
——, of Tietze's syndrome, 249
HORLER, A. R., 56
Hypersensitivity in arthritis, rheumatoid, 1
Hypertension and ACTH, 107
Hypophysis implantation in arthritis, 35

Immunology of connective tissue, 207
Indoxylsulphate, 314
Inflammation, effect of experimental obstructive jaundice in, 309
Iridocyclitis, "rheumatic", 45
Iritis in diagnosis, 50
—— in Reiter's disease, 38
——, "rheumatic", 45
—— with spondylitis, 21
ISDALE, I. C., 69, *70
Isopropanol ammonia, 314
Isotope, radioactive, in assessment of metabolism of connective tissue, 130

Jaundice, Congo red resorption in, 10
——, obstructive, experimental, anti-inflammatory effect of, 309
Joint, finger, involvement of, 26
—— involvement, relation of, to laboratory tests, 25
——, knee, in Reiter's disease, 39
—— lesions in lupus erythematosus, systemic, 111
——, sacro-iliac, in Reiter's disease, 38
——, ——, in spondylitis, ankylosing, 16
—— symptoms in diagnosis, 50
—— tenderness in assessment of arthritis, rheumatoid, 101, 102
JULKUNEN, H., and TIILIKAINEN, A.: Importance of an increased gamma globulin level in the determination of Gm groups in collagen diseases, 318

KEECH, M. K., 142
KEELE, C. A., 143
KEGEL, M. M., 144
KEHR, M.: Comparison of intra-articular cortisone analogues in osteo-arthritis of the knees, 325
KELLGREN, J. H., 60, 98 *bis*, 145, 146, 147, 259, 261, 330, 331
KELLY, M., 144
*KENDALL, P. HUME, 264
KERSLEY, G. D., 263
Kidney in gout, 146
KING, A. J., 145, 146
Knee in lupus erythematosus, systemic, 112

Knee, osteo-arthritis of, cortisone analogues in, 322
—— in Reiter's disease, 39
KRÁLÍK, V.: *see* LENOCH, F., etc., 45
KUIPERS, R. K. W., 259
Kveim test in differential diagnosis, 51

Laboratory tests in diagnosis, 50
—— —— Reiter's disease, 39, 40
LANDON, J., and MALPAS, J. S.: Tietze's syndrome, 249
Latex agglutination test, 255
—— —— —— compared with L.E. cell test, 256
——-fixation test, 146, 322
—— particle inhibition test, 302
—— suspension, British, in agglutination tests, 301
LAWRENCE, J. S., 66, 142
L.E. cell test compared with latex-agglutination test, 256
—— —— in diagnosis, 50
LENNANE, G. A. Q., 144 *bis*
LENOCH, F., KRÁLÍK, V., and BARTOŠ, J.: "Rheumatic" iritis and iridocyclitis, 45
LEPPÄNEN, V. V. E.: *see* Oka, M., etc., 313
L'ESTRANGE ORME, C. R., 261
Leukaemia with cryoglobulins, Congo red resorption in, 10
—— in differential diagnosis, 51
LEWIS, M., 62
Liberia, epidemiology of arthritis, rheumatoid in, 305
Ligue européenne contre le rhumatisme, IV Rheumatological Congress, Istanbul, 1959, 68, 149, 332
LLOYD, A. G., 142
LOEWENTHAL, H., 147
LOEWI, G.: Urinary excretion of acid polysaccharide in rheumatoid arthritis and other diseases, 239
L-tryptophan, 314
Lupus erythematosus, Congo red resorption in, 10
—— ——, disseminated, anti-nuclear factor in, 261
—— ——, gamma globulin in, 319
—— ——, rash in, 50
—— ——, systemic, lesions of joints and tendon sheaths in, 111
—— ——, ——, serum complement in, 215
Lymphoma in differential diagnosis, 51

*MCCREANOR, J. D., 70
MCMINN, F. J., and BYWATERS, E. G. L.: Differences between the fever of Still's disease and that of rheumatic fever, 293
MALAWISTA, S. E., BOIES, L. R., JR., and SEIDES, S. W.: Evaluation of an epidemiological method as applied to rheumatoid arthritis in Liberia, 305
MALPAS, J. S.: *see* Landon, J., etc., 249
Marrow iron in arthritis, rheumatoid, 57
MASON, R. M., 145
—— and WENLEY, W. G.: Treatment of rheumatoid arthritis by a sanatorium regime. The Black Notley experiment, 91
Mechanism of salicylate therapy, 299
Medical Research Council and Nuffield Foundation Joint Committee: A comparison of prednisolone with aspirin or other analgesics in the treatment of rheumatoid arthritis, 173
Metabolism, connective tissue, and limb atrophy, 129
—— studies by chromatography, 313
MEYER, R. K.: *see* ENGERMAN, R. L., etc., 309
MILNE, M. D., 330
Morbidity from rheumatism, acute, in young men, 286
MORGAN, G.: Comparative study of the haemagglutination test and a simple latex-fixation test for the detection of the rheumatoid factor, 322
Morning stiffness in assessment of arthritis, 50, 281
MOSES, V., 143
Myeloma in differential diagnosis, 51

N-acetyl-p-aminophenol (NAPAP) in arthritis, rheumatoid, 190, 197
Nephropathy, familial hyperuricaemic, 262
Netherlands, mobile physiotherapy units in, 260
Neuro-arthropathy, 51
Nodules in diagnosis, 50
Nucleoprotein-latex agglutination test in connective tissue disorders, 255
—— —— —— compared with L.E. cell test, 256
Nuffield Foundation and Medical Research Council Joint Committee on clinical trials, 173
NEWNS, G. R.: *see* Fladee, H. W., etc., 120
New York Rheumatism Association, Officers, 1959, 149
New Zealand Rheumatism Association, 69, 144

OATES, J. K., and CSONKA, G. W.: Reiter's disease in the female, 37
Oedema in diagnosis, 50
OKA, M., and LEPPÄNEN, V. V. E.: Urinary indoles and other "Ehrlich's reagent reactors" in rheumatoid arthritis, 313
OSMOND-CLARKE, H., 98
Osteo-arthritis of knee, cortisone analogues in, 322
—— studies, 143
Osteo-arthropathy, pulmonary, 51
Osteo-articular reactions to prostatectomy, 263
Osteoporosis, spinal, during steroid therapy, 69
OTTEN, H. A., and BOERMA, F. WESTENDORP: Significance of the Waaler-Rose test, streptococcal agglutination, and antistreptolysin titre in the prognosis of rheumatoid arthritis, 24

Pain in diagnosis, 50, 143
"Panadol": *see* N-acetyl-p-aminophenol (NAPAP)
Pan-Pacific Rehabilitation Conference, 144
PARKINS, R. A., and BYWATERS, E. G. L.: Resorption of intracutaneously injected Congo red, 8
Pathogenesis of arthritis, rheumatoid, hypersensitivity in, 1
Periarteritis nodosa, histology of, 50
Periostitis in Reiter's disease, 39
Phenylbutazone in arthritis, rheumatoid, 190, 197
—— derivative (G27 202), controlled trial of, in arthritis, rheumatoid, 244
—— in spondylitis, ankylosing, 23, 145
Physiotherapy unit, mobile, in the Netherlands, 260
Pituitary tissue injection in arthritis, rheumatoid, 34
PLATT, G., *55
*Polyarthritic syndrome (symposium), 148
Polysaccharide, sulphated, in limb atrophy, 130
Polyserositis and Congo red resorption, 10
POPERT, A. J., 63
——: *see* Hajnal, J., etc., 189
Population studies, 142, 305
PORTER, I. H., 62
Precipitin test for rheumatoid factor, 218
Prednisolone compared with aspirin or other analgesics, 173
—— compared with cortisone, 120
—— therapy, statistical analysis of results of, 191, 195
Pregnancy and spondylitis, ankylosing, 21
Prognosis of arthritis, rheumatoid, serological laboratory tests for, 24
Prophylaxis of rheumatism, acute, 290
Prostatectomy, osteo-articular reactions after, 263
Pyrazoles and steroids in therapy of arthritis, 259

Radiology of arthritis, rheumatoid, in clinical trials, 178
—— in assessment of arthritis, familial, 281
—— in diagnosis, 50
—— of Reiter's disease, 38
—— of spondylitis, ankylosing, 16
RAGAN, C.: Role of hypersensitivity in the pathogenesis of rheumatoid arthritis (Heberden Oration, 1958), 1
Rash in differential diagnosis of disseminated lupus erythematosus, 50
Reiter's disease, 51, 145
—— —— in the female, 37
Respiratory infection and rheumatism, acute, 288
Rheumatic fever: *see* Rheumatism, acute
—— syndrome, little known variant of, 69
Rheumatism, acute, fever pattern of, 293
*——, ——, in New Zealand, 70
——, ——, in young men, 285
Rheumatoid arthritis: *see* Arthritis, rheumatoid
—— factor, 3. 215, 322
Rib fusion in spondylitis, 19
RICHARDSON, A. T., 60
RIESZ, E.: *see* FORGÁCS, P., etc., 34
RIX, D., 330
ROBERTSON, D., 143
ROBERTSON, J. D.: *see* Savage, O., etc., 100
ROBINSON, K. C.: *see* Hart, F. Dudley, etc., 15
ROPES, M. W. (chairman): Diagnostic Criteria for Rheumatoid Arthritis (1958), 49
ROSE, B. S., 69
ROSE, F. A., 61
ROSENBAUM, S.: *see* Slater, J. D. H., etc., 285

Salicylate therapy, 25
—— —— and faecal blood loss, 62
—— —— and urinary excretion of acid polysaccharide, 240
Sanatorium regime for rheumatoid arthritis, 91
Sarcoid in differential diagnosis, 51
*SAUNDERS, J. H., 70
SAVAGE, O., 331
——, DAVIS, P. S., CHAPMAN, L., WICKINGS, J., ROBERTSON, J. D., and COPEMAN, W. S. C.: Corticotrophin (ACTH) in rheumatoid arthritis, 100
Scleroderma, diagnosis of, 50
*SCOTT, D. G., 55
——: An immuno-histological study of connective tissue, 207
SCOTT, F. E. T., 65
——: *see* Bywaters, E. G. L., etc., 225, 233
SCOTT, J. T., 330, 331
SEIDES, S. W.: *see* Malawista, S. E., etc., 305
Sequential procedure in testing analgesics, 189, 202
Serology of arthritis, rheumatoid, 24
—— in assessment of arthritis, familial, 280
—— of collagen diseases, 319
—— in diagnosis, 50
—— in estimation of rheumatoid factor, 186, 322
—— of Reiter's disease, 39, 40
Serotonin, 313
Serum complement in rheumatoid disease and S.L.E., 215
—— protein estimation in rheumatoid disease, 216
—— sickness in study of arthritis, rheumatoid, 2
SHADDICK, R. A., 331
SHARP, J., 146
——: *see* HAJNAL, J., etc., 189
Sheep cell agglutination: *see* Agglutination tests
Shoulder-hand syndrome, 51
Side-effects of ACTH therapy, 106, 108
—— of phenylbutazone therapy, 245
—— in steroid therapy, 126
—— —— and aspirin therapy, 182
Skin lesions in differential diagnosis, 51
—— response to Congo red, 8
—— —— to (Trafuril) ester of nicotinic acid in arthritics, aspirin and, 37
SLACK, H. B.: *see* Brooke, J. W., etc., 129
SLATER, J. D. H., and ROSENBAUM, S.: Acute rheumatic fever in young men, 285
SMITH, M. J. H.: Salicylates and the adrenal cortex, 298
SMITH, W. D.: *see* FLADEE, H. W., etc., 120
SOCIETIES:
Australian Rheumatism Association, 144
—— —— Council, 144
British Association of Physical Medicine, 259, 264
—— Medical Association, 148
—— Rheumatic Association, 149
Canadian Rheumatism Association, 148, 329
Empire Rheumatism Council, 142
European League, 68, 149, 332
Heberden Society, 55, 61, 145, 259, 330
New York Rheumatism Association, 149
New Zealand Rheumatism Association, 69, 144
Società italiana di reumatologia: Award of Acqui Prizes, 1959, 68, 264
Turkish Association for Rheumatism Research and Treatment, 149, 332
Soldiers, young, rheumatic fever in, 287
Spine, radiology of, in arthritis, rheumatoid, 184
Splint-making with plastic "Durafoam", 261
Spondylitis, ankylosing, 145
——, ——, gamma globulin in, 319
——, ——, iritis and, 45
——, ——, pyrazoles and steroids in, 259
——, ——, review of, 69
——, ——, symptomatology of, 16
——, ——, in women, 15
*Spondylosis, cervical, 70
SQUIRE, J., 143
STANBURY, S. W., 63
Statistical method of testing analgesics: sequential procedure, 189, 202
STEINBERG, V. L., 146
Steroid therapy, clinical trials of, 120, 173
—— —— and Congo red resorption, 9
—— ——, osteoporosis, spinal, in, 69
—— —— and pyrazoles in arthritis, 259
Stiffness in diagnosis, 50
Still's disease, fever, pattern of, 293
—— ——, fractures in, 330
—— ——, Rose-Waaler titre in, 65
Stress in arthritis, rheumatoid, 2
Surgery in rheumatic disease, 69
—— of wrist and hand in arthritis, rheumatoid, 29
SWANSON, J. NORRIE, 261
Synovectomy in arthritis, rheumatoid, 96
Synovial fluid, irritant substance in, 69
—— tissue in lupus erythematosus, systemic, 112

Tendon lesions in rheumatoid hand, 147
—— sheath lesions in lupus erythematosus, systemic, 111, 115
—— surgery of hand in arthritis, 30
THOMAS, J., 142
THOMPSON, M., 60

Thumb, surgery of, in arthritis, 30
Thyroid and experimental inflammation, 310
Tietze's syndrome, 249
TIILIKAINEN, A.: *see* JULKUNEN, H., etc., 318
Tophus in diagnosis, 50
Toxicity of drugs in arthritis, rheumatoid, 195, 196
Trafuril, effect of aspirin on skin response to in arthritics, 37
Triamcinolone, 59, 122
TRUELOVE, L. H., and DUTHIE, J. J. R.: Effect of aspirin on cutaneous response to the local application of an ester of nicotinic acid (Trafuril), 137
Turkish Association for Rheumatism Research and Treatment, Officers, 1959, 149, 332
*TWEED, J. MOORE, 70 *bis*

Ulceration, peptic, and therapy of arthritis, rheumatoid, 184
Urinary indoles in arthritis, rheumatoid, 313
Urine, excretion of acid polysaccharide in arthritis and 239
Uveitis with arthritis, 145

VALKENBERG, H. A., 262
Vasculitis as primary lesion of arthritis, rheumatoid, 2
VAUGHAN-JACKSON, O. J., 147
Venereal disease and diagnosis of arthritis, 307
*Vital capacity in arthritis, rheumatoid, 70

Waaler-Rose test in arthritis, rheumatoid, prognosis of, 24, 26, 65, 146
*WEDLICK, L., 144
Weight increase, 108
WEIR, D. M., 143
WENLEY, W. G.: *see* Mason, R. M., etc., 91
WEST, H. F., 59, 98
——: *see* Fladee, H. W., etc., 120
WICKINGS, J.: *see* Savage, O., etc., 100
WIGLEY, R. G., 69
*WILKINSON, D. S., 55
WILKINSON, M. C., 97, 143
*WRIGHT, V., 55 *bis*
Wrist, surgery of, in arthritis, 29

Young men, acute rheumatism in, 285

5-hydroxy-indole acetic acid, 313
5-hydroxy-tryptamine, 313
17(OH)CS excretion and response to ACTH, 103

INDEX TO SUBJECTS OF ARTICLES ABSTRACTED

* indicates that only the title of the article is given

Acid, adenosine-5-monophosphoric, in osteo-arthritis of the spine, *81
—, amino, metabolism in arthritis, rheumatoid, *269
—, deoxyribonucleic (DNA), 85, 167, 272
—, glutamic-oxalacetic transaminase (GOT), *169
—, hyaluronic, and colloid osmotic pressure of synovial fluid, *275
—, ——, production by synovial cells, *350
— mucopolysaccharide of human thrombocytes, *351
—, osmic, in arthritis therapy, *270
—, p-toluene sulphonic, test for lupus erythematosus, 84, 272, *276
—, uric, blood level of, *84
—, ——, in gout, 162, *163
—, ——, testicular factors and, *271
Acrosclerosis and scleroderma, 345, 346
ACTH with cortisone acetate in arthritis, rheumatoid, 336
— and phenylbutazone, *342
—, side-effects of, *89
— in spondylitis, ankylosing, *270
Adenomatosis, malignant pulmonary, in scleroderma, 345
Adrenal cortex in arthritis, rheumatoid, 336
— —, Itsenko-Cushing disease and, 352
— —, obesity and, 352
— —, triamcinolone and, 352
— hormones, *354
Adrenocortical excretion in arthritis, rheumatoid, *88
Aetiology of rheumatism, focal-sepsis theory, *90
Agglutination of collodion particles sensitized with rheumatoid serum, *157
—, leucocyte, inhibition by L.E. serum, 166
— test, 79 *bis*, 80, 347 *bis*, 348
— — in experimental bone and joint infections, *88
— —, serial, in arthritis, rheumatoid, 154
— — in spondylitis, ankylosing, *270
Ageing and osteo-arthritis, *338
Alkali, intra-articular, in osteo-arthritis, *269
Alligator erythrocyte sedimentation test in detection of rheumatoid factor, *274
Alpha-chymotrypsin in scapulo-humeral periarthritis, *270
Amyloidosis in chronic polyarthritis, 269
— secondary to arthritis, rheumatoid, regression of, 267
Anaemia in arthritis, iron therapy of, *268
—, auto-immune haemolytic, complicating lupus erythematosus, splenectomy in, 343
Ankylosing spondylitis: *see* Spondylitis, ankylosing
Ankylosis, fibrous, of finger joints in arthritis, rheumatoid, *157
Antibiotics with corticosteroids, 353
— in rheumatology, *171
Anticoagulants, circulating, in lupus erythematosus, *351
Antihyaluronidase activity, experimental, of antirheumatic drugs, *278
Antimalarials in arthritis, rheumatoid, *81, *268 *bis*
— in rheumatology, *171
— in Sjögren's syndrome, 341
—, synthetic, in arthritis, rheumatoid, *338
Antistreptolysin and Waaler-Rose test, *275
Aorta, lesions of, in spondylitis, ankylosing, *159, *270
Arteritis after use of cortisone, 276
Arthritis, bacterial, *270
—, crico-arytenoid, 273
—, degenerative, of lumbo-sacral joint, *270
—, dextro-amphetamine as analgesic in, *270
—, electromyography in, 341
—, experimental, cortisol and, *88
—, ——, phenylbutazone and, *88
—, ——, in swine, hydralazine for, *273
—, gouty, *343
— of hand, 340
—, hexylresorcinol in, 160
—, intra-articular steroids in, 160
—, — therapy of, *83
— and myocardial infarction, 341
—, osmic acid in, *270
—, pain in, relieved by sympathetic denervation, 340
—, phenylbutazone in, 160
—, physiotherapy in, 162
— and psoriasis, *86
—, ——, triamcinolone in, *158
—, rheumatoid, ACTH with cortisone acetate in, 336
—, ——, activity of, and plasma 17-hydroxycorticosteroids during and after pregnancy, 268
—, ——, adrenal cortical activity in, 336
—, ——, agglutinating factor, demonstration of, 80
—, ——, agglutination tests in, *168 *ter*
—, ——, amyloidosis secondary to, regression of, 267
—, ——, antiglobulin factors of, and those in antibacterial immune sera, *275
—, ——, antimalarials in, *81, *268 *bis*
—, ——, ——, synthetic, in, *338
—, ——, arthroplasty of hip in, *338
—, ——, Bentonite flocculation test, 274 *bis*, *275, 337
—, ——, in children, 155, *157, *158
—, ——, chloroquine in, 77, 78 *ter*, *81, 153, *157
—, ——, cholinesterase activity in, *275
—, ——, as collagen disease, *269
—, ——, corticosteroids in, *268
—, ——, ——, and peptic ulceration, 78
—, ——, ——, and skin response to ultra-violet light, 270
—, ——, cortisone, long-term, in, *158
—, ——, dexamethasone in, *158
—, ——, differential diagnosis of, *268
—, ——, digestive problems in, *81
—, ——, electromyography of, *269
—, ——, evaluation of, 267
—, ——, experimental, infective aetiology of, *268

Arthritis, rheumatoid, feet in, *81
——, ——, gold therapy in, 77 *bis*, *157, *268
——, ——, heart involvement in, 80, 155, *269
——, ——, hypersensitivity in, *268
——, ——, immuno-electrophoresis of, *275
——, ——, intra-articular hydrocortisone in, 76 *bis*, *270
——, ——, ——, injections in, *157
——, ——, iproniazid in, 335
——, ——, iron therapy of anaemia in, *268
——, ——, isoniazide and prednisone in, *269
——, ——, juvenile, *268, 336
——, ——, kidney in, *81, *274
——, ——, laboratory tests for 166 *ter*, 167, 337, 348 *bis*
——, ——, laryngeal stridor in, 80
——, ——, latex-fixation tests for, *81, 337
——, ——, mepacrine in, 78
——, ——, metabolism of amino acids and proteins in, *269
——, ——, methylprednisolone in, *347
——, ——, and osteo-arthritis, *158
——, ——, pathology of, *275
——, ——, periodic assessment of, *157
——, ——, peripheral neuritis in, *269, 337
——, ——, —— vascular changes in, *347
——, ——, "Pipradrol" in, *269
——, ——, pituitary basophils in, 157
——, ——, prednisone in, *158 *ter*
——, ——, —— and isoniazide in, *269
——, ——, prevention of invalidism in, *337
——, ——, primaquine in, 78
——, ——, probenecid in, *158
——, ——, psychological effects of "Pipradrol" in, *269
——, ——, psychosocial studies of, *338
——, ——, radiology of, 339
——, ——, rehabilitation, medical, of, *269
——, ——, respiratory function in, *269
——, ——, senile, *268 *bis*
——, ——, sepsis in, *338
——, ——, serial haemagglutination tests in, 154
——, ——, serology of, *81, *87, *88 *bis*, 266, 349 *bis*, *350, *351 *sext*
——, ——, and Serotonin, response to, 354
——, ——, serum proteins in, *275
——, ——, —— response in, *337
——, ——, side-effects of prednisone in, *338
——, ——, steroid therapy of, 154
——, ——, synovial fluid in, *81, *269
——, ——, —— —— hyaluronate in, 348
——, ——, systemic, *338
——, ——, triamcinolone in, 75 *bis*, *158 *bis*, 335
——, ——, variants of, 155
——, splints in, *83
Arthroplasty of hip, *338
Arthrosclerosis, *159
Aspirin, intestinal bleeding after, 171
Auricular appendage, rheumatic process of, 165, *351

Bacteriology of rheumatism, acute, 333
Balneotherapy of osteo-arthritis, *269
Benemid: *see* Probenecid
Bentonite flocculation test, 274 *bis*, *275, 337
Biopsy of knee, 161
Blennorrhoea, *342
Blood culture studies of rheumatism, acute, 72
—— disease, malignant, rheumatoid syndromes in, *90
—— dyscrasias and gout, *343
——, occult, in faeces after aspirin therapy, 171
—— uric acid level, *84
Bones, finger, demineralization of, *157
Bornholm disease, myalgia in, *278
Bracing in arthritis, rheumatoid, *338
Brain lesions and rheumatism, *278
Brucellosis and spondylitis, 159

Cancer of lung and rheumatism, *278
Caprokol: *see* Hexylresorcinol
Capsulitis of shoulder, *83
Carbohydrate metabolism and dexamethasone, *354
Cardiopathy in children, *75
Carditis, rheumatic, with atrial septal defect, 335
——, ——, auricular appendages in, *351
——, ——, laboratory findings during treatment with hormones of, 73
——, ——, short-term hormone therapy in, 334
——, valvular, penicillin in, 333
——: *see also* Heart
Children, arthritis in, 155, *157, *158, *338 *bis*
——, rheumatism in, 334
——, ——, acute, in, 75, 150, *152 *quater*, *153
——, streptolysin reactions in, *75
Chloroquine in arthritis, rheumatoid, 77, 78 *ter*, *81, 153, *157
—— in collagen disease, *273
—— after gold therapy, haemagglutination and, *275
—— in lupus erythematosus, 343
Chlorpromazine in disengagement from steroid therapy, *81
Cholinesterase activity in arthritis, rheumatoid, *275
Chorea, rheumatic, reserpine in, *266
——, Sydenham's, 151
Chromatography of L.E. factor, 165
—— of rheumatoid factor, *351
Climacteric, osteo-arthritis at, *269 *bis*
Climate and rheumatism, *278
Collagen disease, *164 *bis*
—— ——, arthritis, rheumatoid, as, *269
—— ——, chloroquine in, *273
—— —— and digestive disorders, *86, *347
—— ——, intravenous procaine in, 272
—— ——, lung in, *86
—— ——, mucinolysis in, 85
—— ——, pulmonary symptoms of, 272
—— —— and reaction diseases, *273
—— ——, respiratory manifestations of, 85, *273
—— proteins, soluble, antigenic properties of, *275
—— ——, ——, —— affinity with serum proteins, *275
Congo red test, intracutaneous, 166
Connective tissue disease, *164, *347 *bis*
—— —— ——, serology of, *88
—— ——, histiocapillary unity, and rheumatism, *276
—— ——, loose, cortisol metabolism by, 88 *bis*
Corset, plaster, *83
Corticosteroids with antibiotics, 353
—— in rheumatism, acute, 74
——, 16α-methyl, appraisal of, 76
Cortisol and arthritis, experimental, *88
—— and gastric ulcer, experimental, 88
—— metabolism by loose connective tissue, 88 *bis*
Cortisone acetate with ACTH in arthritis, rheumatoid, 336
——, arteritis after use of, 276
——, hyperglycaemia during treatment with, *88
——, intestinal perforation after use of, 276
——, long-term, in arthritis, rheumatoid, *158
—— and lymphocyte size, *275
—— in rheumatism, acute, 151, 152
—— ——, ——, visceral side-effects of, 266
C-reactive protein, *169 *bis*

C-reactive protein and erythrocyte sedimentation rate in rheumatism, acute, 74
Creatinuria in arthritis, rheumatoid, *87
Cryoglobulins in lupus erythematosus, *169
Cushing's syndrome, radiological changes in, 88
Cyst, synovial of hip, *338

"Decortin-H": *see* Prednisolone
Demineralization of finger bones in arthritis, rheumatoid, *157
Denervation, sympathetic, for relief of arthritic pain, 340
Deoxyribonucleic acid (DNA) complement-fixation in S.L.E., 167
——-protein sensitization, collagen disease and, 85
—— and serum factor, precipitin reaction of, in lupus erythematosus, systemic, 272
Dermato-arthritis, lipoid, *164
Dermatomyositis, dexamethasone in, *273
——, malignancy and, *347
——, rheumatic signs of, 346
—— and sensitization to DNA-protein, 85
——, serum transaminase activity in, *164
Dexamethasone, *162, 352, 353 *bis*, *354 *bis*
—— in arthritis, rheumatoid, *268
—— in dermatomyositis, *273
——, effects of, 170, 276
——, ——, compared with prednisone, *277
Dextro-amphetamine-analgesic combination in arthritis, *270
Diabetes and gout, 271
Disk, intervertebral, hernia of, *83
——, lumbar, disability due to degeneration of, *270
——, ——, herniation, *270
—— syndrome, *83
Disseminated sclerosis: *see* Sclerosis, multiple
Donaggio's reaction in inflammatory rheumatism, *169
Dupuytren's contracture, histology of, 83
"Durafoam" splints, *83

Electrocardiography of scleroderma, *164
Electro-encephalography of collagen disease, *164
Electromyography in arthritis, rheumatoid, *269, 341
—— in collagen disease, *164
Electrophoresis of L.E. factor, 165
—— in serology of arthritis, rheumatoid, 349, 350 *bis*
—— of serum proteins in rheumatism, acute, *153
Endomyocarditis in rheumatism, acute, treated with cortisone, 152
Enzymes, serum, in rheumatism, acute, 151
Erythema nodosum, 340
Erythrocyte sedimentation rate, *169
—— —— —— and C-reactive protein in rheumatism, acute, 74
—— —— —— in normal children, 86
—— —— ——, sodium citrate and potassium ammonium oxalate and, 87
Eyes in collagen disease, 163, *164
—— in periarteritis nodosa, 273
—— in spondylitis, ankylosing, 82

Familial incidence of rheumatoid factor, 153, *275
Feet, arthritis, rheumatoid of, *81
Felty's syndrome, *268
Fever, rheumatic: *see* Rheumatism, acute
Fibrinogen polymerization test, *351
"Fibrinoid" change, lesions of, 87
"Fibrositis", *278
Finger joints in arthritis, rheumatoid, *157 *bis*
Focal infection, aetiology of arthritis, *90, *268
Fuhl precipitin reaction and sheep cell agglutination, 79

Gamma globulin in latex-fixation test, *275
—— —— in rheumatoid factor, 79 *bis*
Glutamic-oxalacetic acid transaminase (GOT) in rheumatic subjects, *169
Gold therapy in arthritis, rheumatoid, 77 *bis*, *157 *bis*, *268
—— —— with chloroquine, effect of, on haemagglutination, *275
Gout, *343 *quater*
—— and blood dyscrasias, *343
—— and diabetes, 271
——, female, *163
——, —— Negro, *84
——, fractionation of urinary 17-ketosteroids in, *275
——, lithiasis, urinary, in, *163
——, metabolism of, *163
——, physiopathology of, *343
——, precipitation of attacks of, *271
——, probenecid in, *271
——, radiology of, *84 *bis*
——, serum uric acid in, 162
——, uricosuric action of G.28 315 in, *271
——, G.28 315 in, 342
G.27 202, 341
G.28 315 in gout, *271, 342

Haemagglutination: *see* Agglutination
Haemolytic streptococcal infection in arthritis, experimental, *268
Haemophilia, pathology of, *274
Hand in arthritis, *157 *ter*, 340
—— in scleroderma, *273
Heart disease, rheumatoid, *269
—— ——, valvular, penicillin in, *153
—— ——, ——, and spondylitis, *82
—— involvement in arthritis, rheumatoid, 80, 155
—— in lupus erythematosus, *273
—— in scleroderma, *165
——: *see also* Carditis
Heparinaemia and heparin tolerance in juvenile rheumatic fever, *275
Hepatitis, lipoid, 343
Heredity in spondylitis, ankylosing, 338
Herpes zoster, *354
Hexadecadrol: *see* Dexamethasone
Hexylresorcinol in arthritis, 160
Hip arthroplasty in arthritis, rheumatoid, *338
—— motion, measurement of, *354
——, osteo-arthritis of, *338, *158, *159 *ter*
——, —— of, intra-articular alkali therapy in, *269
——, ——, McMurray's osteotomy of, *158
——, pseudopolyarthritis of, 161
——, rheumatoid synovial cyst of, *338
Histamine and polysaccharide system of blood serum, *350
Histone in lupus erythematosus antinuclear reaction, *276
Homeostasis between cortisone in Noradrenalin, *157
Hormone therapy of carditis, rheumatic, laboratory findings in, 73
—— —— ——, ——, short term, 334
—— —— of rheumatism, acute, 150
Hyaline membrane, pulmonary, in pneumonia, "rheumatic", 73
Hyaluronidase and synovial proteins, *87
Hydralazine in experimental arthritis in swine (L.E. syndrome), *273
Hydrarthrosis, *354
Hydrocortancyl injections, *277
Hydrocortisone and electrophoresis, *350

Hydrocortisone injections, 76 *bis*, 89, *277
——, intra-articular, and joint temperature, *270
Hydroxychloroquine in lupus erythematosus, 343
Hypercortisonism, 170
Hyperglycaemia during cortisone therapy, *88
Hypersensitivity in patients with arthritis, rheumatoid, *268

Immuno-electrophoresis in locating C-reactive protein, *169
—— of rheumatoid serum, *87, *275
Immuno-histochemistry of fibrinoid lesions, *87
Immunology of rheumatoid factor, *275, *351
Infection, experimental, in rats, and haemagglutination reaction, *88
Inflammation in osteo-arthritis, *159 *quinter*
Injections, intra-articular, in osteo-arthritis of knee, 158
——, ——, of steroids in arthritis, 160
Insurance and rheumatism, *278
Intestines, disorders of, in rheumatism, *278
——, perforation of, after use of cortisone, 276
Intracutaneous stimulation in treatment of rheumatism, *172
Invalidism, prevention of, *337
Iproniazid in arthritis, rheumatoid, 335
Irgapyrine, side-effects of, *89
Iron therapy of anaemia in arthritis, rheumatoid, *268
Isoniazide with prednisone in arthritis, rheumatoid, *269
Itsenko-Cushing's disease, 352

Joint, degenerative disease of, orthopaedics in, *158
——, finger, in arthritis, rheumatoid, *157 *bis*
—— infections after steroid therapy, *354
——, lumbo-sacral, arthritis of, *270
——, sacro-iliac, lesions of, *82
—— symptoms with panniculitis, *172
—— temperature and intra-articular hydrocortisone, *270
——, temporomandibular, disease of, head and neck pain in, 83

Keratosis blennorrhagica, *342
Kidney in arthritis, rheumatoid, *81, *274
——, blood vessels of, in rheumatism, 168
—— in Schönlein-Henoch disease, *86
—— in scleroderma, 163
Knee, osteo-arthritis of, *81, *338
——, ——, intra-articular alkali in, *269
——, ——, —— "Decortin-H" in *269
——, ——, —— injections in, 158
——, punch biopsy of, 161

Laboratory diagnosis of arthritis, rheumatoid, 348
Laryngeal stridor in arthritis, rheumatoid, 80
Latex-agglutination test for disseminated lupus erythematosus, 167
Latex-fixation test, 166 *bis*, 347 *bis*, *351 *quater*
—— —— in arthritis, rheumatoid, *81, *168, 337
—— ——, human gamma-globulin as reactant in, *275
—— and L.E. cell tests, *87
—— —— "Periston", 87
—— —— and Waaler-Rose test, *275
L.E. cell tests and latex-fixation, *87
—— factor, 273
—— ——, chromatography of, 165
—— ——, electrophoresis of, 165
—— ——, serology of, *276
—— phenomenon, *86, 165, 166, 168, *276 *bis*
Leucocyte agglutination, 166, 167
Leukaemia, articular signs of, *162
——, pseudo-rheumatic, *278
Ligament relaxation in osteo-arthritis, *269
Lipman-Sachs disease: *see* Lupus erythematosus, disseminated
Lithiasis, urinary, in gout, *163
Lugol's iodine reaction, *172
Lumbago, traumatic, *354
Lung in arthritis, rheumatoid, *164
—— cancer and rheumatism, *278
—— in collagen disease, *86, 272
——, honeycomb, and adenomatosis, malignant pulmonary, in scleroderma, 345
—— in lupus erythematosus, *164
Lupus erythematosus, blood picture of, *276
—— —— and cardiovascular disease, aetiology of, *347
—— ——, cryoglobulins in, *169
—— ——, diagnosis of, *349
—— ——, disseminated, *86 *bis*, *273
—— ——, ——, adrenocorticoids in, 344
—— ——, ——, latex-agglutination test for, 167
—— ——, ——, oedematous forms of, *164
—— ——, ——, p-toluene sulphonic acid test in, *276
—— ——, ——, renal forms of, *164
—— ——, ——, and sensitization to DNA-protein, 85
—— ——, ——, Widal reaction in, *164
—— ——, hepatic lesions of, 343
—— ——, histone in antinuclear reaction of, *276
—— ——, methyl prednisone in, *347
—— ——, quinacrine, hydroxychloroquine, and chloroquine in, 343
—— ——, serology of, *351 *ter*
—— ——, systemic, *86 *ter*
—— ——, ——, cardiovascular changes in, *273
—— ——, ——, in childhood, *164
—— ——, ——, diagnosis of, 163
—— ——, ——, pleuritis in, 84
—— ——, ——, precipitation test for, 272 *bis*, 273
—— ——, ——, p-toluene sulphonic acid test for, 84
—— ——, ——, pulmonary signs of, *164 *bis*
—— ——, ——, serology of, 163
—— ——, ——, and Sjögren's syndrome, 271
—— ——, ——, triamcinolone in, 164
—— globulin-nucleo-histone interaction, 167
Lutembacher's syndrome, 335
Lymphocyte size in arthritis, rheumatoid, treated by cortisone, *275

McMurray's osteotomy in osteo-arthritis of hip, *158
Macroglobulins and connective tissue disease, *350
Membrane, synovial, histology of, 348
Mepacrine in arthritis, rheumatoid, 78
Methyl prednisolone in arthritis, rheumatoid, *347
—— —— in lupus erythematosus, *347
Minnesota, children with rheumatism, acute, in, *152
Morbidity from rheumatism in Sydney, 277
Mucinolysis in collagen disease, 85
Mucoproteins, *169
——, urinary, *351
Multiple sclerosis: *see* Sclerosis, multiple
Muscles in spondylitis, ankylosing, 82
Myalgia in Bornholm disease, *278
——, functional, *278
Myocardial infarction and arthritis, 341 *bis*

Negro, gout in, *84
Nephritis and rheumatism, 265
Nervous system in periarteritis nodosa, *273
Neuritis, peripheral, in arthritis, rheumatoid, *269, 337

Neurology of spondylosis, *270
Neuro-psychiatric side-effects of steroid therapy, 170, *171

Obesity and adrenocortical function, 352
Oedema in lupus erythematosus, *164
Oesophagus in scleroderma, *164, *165
Orthopaedics of degenerative joint disease, *158
Osteo-arthritis, *81 *quater*
—— and arthritis, rheumatoid, *158
——, balneotherapy of, *269
—— of cervical spine, *271
—— at climacteric, *269 *bis*
—— of hip, *338
——, inflammatory signs of, *159 *quinter*
——, intra-articular alkali therapy in, *269
——, —— hydrocortisone in, *270
——, —— prednisolone in, *269
—— of knee, *338
—— ——, intra-articular injections in, 158
——, ligament relaxation in, *269
——, lumbar, *338 *bis*
——, organic protein lysates in therapy of, *269
——, pain in, *158
——, phenylbutazone in, *269
—— prophylaxis, *338
—— of sterno-clavicular joint, *338
——, tuberculin therapy of, *338

Pain, arthritic, sympathetic denervation of relief of, 340
Panniculitis with joint symptoms, *172
——, subacute nodular migratory, 340
Pathogenesis of rheumatism, *278
Penicillin in carditis, valvular, 333
—— in rheumatism, acute, *153 *bis*, 266, 333
Peptic ulcer during steroid therapy, 170, *171
Periarteritis nodosa, 271
—— ——, eyes and, 273 *bis*
—— ——, gastroenterology of, *165
—— ——, nervous system and, 273
—— ——, steroid therapy of, *165
Periarthritis, scapulo-humeral, alpha-chymotrypsin in, *270
"Periston" latex-fixation test, 87
Phenylbutazone, 160, 171 *ter*, 341, *342 *ter*
—— in arthritis, experimental, *88
—— in osteo-arthritis, *269
—— with prednisone, *171
—— and serum polysaccharide protein ratios, *88
—— and Stevens-Johnson syndrome, *342
Physiotherapy in arthritis, 162
"Pipradrol", psychological effects of, in arthritis, rheumatoid, *269
Pituitary basophils in arthritis, rheumatoid, 157
Plasma corticosteroids and ACTH after prolonged steroid therapy, *277
—— 17-hydroxycorticosteroids in rheumatism, 277
—— —— in arthritis, pregnancy and, 268
Pleuritis in systemic lupus erythematosus, 84
Pneumonia, interstitial, in rheumatic disease, *354
——, "rheumatic", *350 *bis*
——, ——, with pulmonary hyaline membrane, 73
Polyarteritis nodosa, complications of, 163
Polyarthritis, chronic, amyloidosis in, 269
——, epidemic, *270
——, gouty, *83
Polymyositis, 346, *354
Potassium ammonium oxalate and erythrocyte sedimentation rate, 87
Precipitation test for lupus erythematosus, 272, *273
Prednisone, *162 *bis*, 353
—— in arthritis, rheumatoid, *158 *ter*
—— and dexamethasone, *277
——, digestive disturbances due to, 169
——, intra-articular, in osteo-arthritis, *269
——, intramuscular, *277
—— with isoniazide in arthritis, rheumatoid, *269
——, long-term, in arthritis, rheumatoid, juvenile, 336
—— with phenylbutazone, *171, *342
—— in rheumatism, acute, *75
——, side-effects of, in arthritis, rheumatoid, *338
——, trimethyl, intra-articular, *162
Prednisolone: *see* Prednisone
Pregnancy and 17-hydroxycorticosteroids in arthritis, rheumatoid, 268
Primaquine in arthritis, rheumatoid, 78
Probenecid in arthritis, rheumatoid, *158
—— in gout, *271
Procaine, intravenous, in collagen disease, 272
Properdin in sera in rheumatism, cancer, and normal subjects, *109
——, Zymosan assay of, affected by rheumatoid factor, *275
Prophylaxis of osteo-arthritis, *338
—— of rheumatism, acute, 266 *ter*, *335
Protein lysates, organic, in osteo-arthritis, *269
—— metabolism in arthritis, rheumatoid, *269
—— —— during steroid therapy, 169
—— patterns in serum and synovial fluid, 349, 350 *bis*
——, synovial, and hyaluronidase, *87
Pseudo-polyarthritis of hip, 161
Pseudo-Pott's disease, *338
Psoriasis, *158, *162
—— and arthritis, *86
Psychology of arthritis, rheumatoid, *338
P-toluene sulphonic acid test for systemic lupus erythematosus, 84
Pyrazol derivative in rheumatoid disease, 277

Quinacrine in lupus erythematosus, 343

Radiology of Cushing's syndrome, 88
—— of gout, *84 *bis*
—— of low back pain and disk syndrome, *83
—— of peptic ulceration in arthritis, rheumatoid, treated with corticosteroids, 78
—— of spondylitis, ankylosing, *270
—— of spondylosis, *270
Raynaud's phenomenon, *354
—— —— and scleroderma, 345
Rehabilitation after arthritis, rheumatoid, *269
——, cost of, *172
—— after inflammatory rheumatism, *278
Reiter's disease, *342
—— ——, radiology of, 339
—— ——, sacro-iliitis in, 83, 339
—— —— in Tunisia, 339
Relaxin therapy in scleroderma, diffuse progressive, 344
Reserpine in chorea, rheumatic, *266
Respiration and arthritis, rheumatoid, *269
Retinitis, pigmentary, and periarteritis nodosa, 273
Rheumatic fever: *see* Rheumatism, acute
Rheumatism, acute, in adults and atypical arthritis, *278
——, ——, β-haemolytic streptococcal infection in, 265, 266, 333
——,——, blood culture studies in, 72
——, ——, in children, *75, 150 *bis*, *152 *quater*, *153, 334

Rheumatism, acute, in children, heparinaemia and heparin tolerance in, *275
——, ——, clinical picture of, *75
——, ——, in college students, *266
——, ——, corticosteroid therapy of, 74, 151, 152
——, ——, —— ——, and visceral lesions, 266
——, ——, C-reactive protein and erythrocyte sedimentation rate, 74
——, ——, differential diagnosis of, 72
——, ——, familial, 265, 266
——, ——, fibrinogen polymerization test in, *351
——, ——, hormone therapy of, 150
——, ——, literature of, *152
——, ——, manifestations of, after cessation of therapy, *75
——, ——, mobilization of patients with, *335
——, ——, multiple sclerosis and, *266
——, ——, nephritis and, 265
——, ——, pathology of, *275
——, ——, penicillin in, *153, 266, 333
——, ——, prednisone in, *75
——, ——, prophylaxis of, 71 *bis*, *75, 266 *ter*, *335
——, ——, reserpine in, *266
——, ——, serum enzymes in, 151
——, ——, —— glucoproteins in, 152
——, ——, —— mucoproteins in, 75
——, ——, —— oxalo-acetic transaminase activity in, and salicylate therapy, 74
——, ——, —— proteins in, *350, *351
——, ——, —— —— electrophoresis in, *155
——, ——, spondylitis and, *82
——, ——, streptococcal infection in, morbid anatomy of, *266
——, ——, streptolysin reactions in children with, *75
——, ——, therapy, current status of, *335
——, inflammatory, in children, *338
——, ——, fractionation of urinary 17-ketosteroids in, *275
——, ——, rehabilitation after, *278
——, muscular, *165
Rheumatoid arthritis: *see* Arthritis, rheumatoid
—— factor, *88, 153, 274 *bis*, *275 *bis*
—— ——, chromatography of, *351
—— ——, familial, 153, *275
—— —— in homogenates of articular capsule and blister fluid, *351
—— ——, immunology of, *275
—— ——, interaction of, with antigen-antibody complexes and aggregated gamma globulin, 79
—— ——, pathogenesis of, *351
—— ——, precipitation reaction for, 349
—— ——, uniquely large amounts of, 154
—— —— and Zymosan assay of properdin, *275

Sacro-iliitis in Reiter's disease, *83, 339
Salicylate therapy of rheumatism, acute, and serum oxalo-acetic transaminase activity, 74
Schönlein-Henoch disease, renal involvement in, *86
—— —— purpura, *162
Sciatica due to herniation of disk treated by corset, *83
——, resistant, *342
Scleroderma, acrosclerosis, and Raynaud's phenomenon, 345
——, classification of, *273
——, diffuse progressive, relaxin in, 344
——, digestive tract in, *165
——, electrocardiography of, *164
——, hand in, *273
——, heart in, *165, 345
Scleroderma, honeycomb lung and pulmonary adenomatosis in, 345
——, kidneys in, 345 *bis*
——, lungs in, 346
——, malignant, *347
——, oesophagus in, *164, *165
——, peripheral vascular changes in, *347
——, progressive, *273
——, renal function in, 163
—— and sensitization to DNA-protein, 85
——, treatment of, *164, 346
——, visceral signs of, *347
Scleroneuropathy, *165
Sclerosis, multiple, and rheumatism, acute, 266
Serology of arthritis, rheumatoid, *81, *87, *88 *bis*, 165, 349 *bis*, 350 *quinter*, *351 *sext*
—— of L.E. factor, *276
Serotonin response in rheumatic disease, 354
Serum enzymes in rheumatism, acute, 151
—— factor in lupus erythematosus, 272
—— glycoproteins, 152, *169
—— mucoprotein content in diagnosis and assessment of rheumatism, acute, in children, 75
—— oxalo-acetic transaminase activity in rheumatism, acute, and salicylate therapy, 74
—— polysaccharide/protein ratios, cortisol and, *88
—— —— ——, phenylbutazone and, *88
—— protein in arthritis, rheumatoid, *275
—— —— electrophoresis in rheumatism, acute, *153
—— response in arthritis, rheumatoid, *337
——, rheumatoid factor of, 266
——, ——, immuno-electrophoresis of, *87
—— transaminase activity in dermatomyositis, *164
—— uric acid in gout, 162
Shoulder, capsulitis of, *83
—— hand syndrome and herpes zoster, *354
——, pseudopolyarthritis of, 161
Side-effects of cortisone, 266, 276
—— of dexamethasone, 353, *354
—— of rheumatism therapy, *89
—— of triamcinolone, 276
Sjögren's syndrome, antimalarials in, 341
—— —— and lupus erythematosus, systemic, 271
Sodium citrate and erythrocyte sedimentation rate, 87
—— salicylate, metabolic activity of, *89
Spine, cervical and lumbar, spondylosis of, *270
——, ——, osteo-arthritis of, *271
——, osteo-arthritis of, *81
——, ——, adenosine-5-monophoric acid in, *81
Splenectomy in acquired auto-immune haemolytic anaemia complicating systemic lupus erythematosus, 343
Splinting in arthritis, rheumatoid, *338
Splints, "Durafoam", *83
Spondylitis, ankylosing, 160 *quater*
——, ——, aortic lesions of, 159, *270
——, ——, clinical findings in, *270
——, ——, haemagglutination in, *270
——, ——, heredity in, 338
——, ——, muscle changes in, 82
——, ——, ocular lesions in, 82
——, ——, radiology of, *270, 339
——, ——, treatment of, *270
——, ——, ——, with small doses of ACTH, *270
——, early, physical findings in, *270
——, infective, *82
——, rheumatoid, 81, *82
——, undulant fever in, 159
Sternoclavicular joint, osteo-arthritis of, *338

Steroid therapy of arthritis, rheumatoid, 154, *268 *bis*
—— —— ——, ——, and peptic ulceration, 78
—— ——, intra-articular inflammatory reactions to, *277
—— ——, ——, in tennis elbow, *270
—— —— of periarteritis nodosa, *165
—— ——, problems of, *277
—— ——, prolonged, *354 *bis*
—— —— and sepsis in arthritis, rheumatoid, *338
—— ——, side-effects of, 169, 170 *bis*, *171
—— —— and skin response to ultra-violet light in arthritis, rheumatoid, 270
Stevens-Johnson syndrome caused by phenylbutazone, *342
Still's disease, 155, *157, *338
Streptococcal aetiology of rheumatism, *172
—— infection and rheumatism, acute, 265, *266
Streptococci, group-A β-haemolytic, and rheumatism, acute, 333
Streptolysin reactions in children with rheumatoid, acute, *75
Sulphonamides in prophylaxis of rheumatism, acute, *335
Surgery of hand in arthritis, rheumatoid, *157
Synovial fluid in arthritis, rheumatoid, *81, *269
—— —— ——, ——, colloid osmotic pressure of, 274, *275
—— —— ——, ——, hyaluronate of, 348
—— proteins, 349, 350 *bis*
—— —— and hyaluronidase, *87

Tachycardia, *354
Tendinosis, *165
Tennis elbow, intra-articular corticosteroids in, *270
Tenosynovitis in arthritis, rheumatoid, 156 *bis*
Tetanic crises during steroid therapy, *171
Tietze's syndrome, *83 *bis*, *354
Tissue antigens, complement-fixation with, in rheumatic subjects, 350
Transaminase, *169
—— activity, serum oxalo-acetic, in rheumatism, acute, 74
Trauma and rheumatism, *278 *bis*
Triamcinolone, *162
—— and adrenal function, 352
—— in arthritis, rheumatoid, 75 *bis*, *158 *bis*, 335
—— ——, psoriatic, *158
—— in lupus erythematosus, systemic, 164
——, side-effects of, 276
Tuberculin therapy of osteo-arthritis, *338
Tunisia, Reiter's disease in, 339

Ulcer, gastric, experimental, cortisol and, 88
Ultracortenol: *see* Prednisone
Ultra-violet light, skin response to, in arthritis, rheumatoid, 270
Undulant fever, spondylitis in, 159
Urinary excretion of 17-hydroxycorticosteroids and 17-ketosteroids in arthritis, rheumatoid, 336
—— mucoproteins in rheumatism, *351
Urine, 17-ketosteroid fractionation of, in gout and inflammatory rheumatism, *275

Vasoconstrictor reflex in rheumatic subjects, *172
Vertebral tropho-postural syndrome, painful post-menopausal, *269
Vessels, peripheral, in arthritis, rheumatoid, *347
——, ——, in rheumatism, acute, *152, *153
——, ——, in scleroderma, *347

Waaler-Rose haemagglutination reaction, 80, 347 *bis*, *351
—— —— —— and anti-streptolysin reaction, *275
—— —— —— and latex-fixation test, *275
Weather and rheumatism, *89
Widal's reaction in lupus erythematosus, *164
Women, gout in, *163
Working capacity and rheumatism, *172

Zymosan assay of Properdin affected by rheumatoid factor, *275

5-hydroxytryptamine in human thrombocytes, *351

INDEX TO AUTHORS OF ARTICLES ABSTRACTED

* indicates that only the title of a paper or article is given

*Adams, J. P., 157
*Agrawal, P. L., 269
Ahern, A. M., 160 *bis*
*Aho, A., 164
*Aisenberg, A. C., 276
Albeaux-Fernet, M., 352
Alexander, W. R. M., 163
*Amor, B., 268
*Anderson, S. G., 270
Andreyeva, V. S., 334
Ansell, B. M., 159
Ansell, H. B., 343
Appel, B., 343
*Arcos Pérez, M., 347
Armas-Cruz, R., 163, 344
*Arnaudet, M., 160
*Arndt, H., 276
*Aron, A., 335
Arslan, M., 85
*Ascione, A., 164
Aslaksen, B. B., 269
*Athanasiadou, M. H., 351
Athanasiadou, P. A., 85

Bahn, R. C., 157
Bakos, L., 350
*Balina, L. M., 342
Ballabio, C. B., 170, *343
Banerjee, S. K., 270
*Banos, J. G., 270
*Barahona, R., 86
*Barbieri, M., 347
*Barceló, P., 169, 171
Bardawil, W. A., 85
*Barros, B., 157
Barroso-Moguel, R., 74, 151, 152, 266
Bartholomew, L. E., 157
*Barzin, J., 160
Bayles, T. B., 85
*Baylon, H., 273
*Bednár, B., 266
*Behr, G., 166
*Beickert, A., 351
*Belart, W., 158
*Bellows, M. T., 75
*Bereston, E. S., 342
*Bergami, P., 269
*Berglöf, F. E., 270
*Berkowitz, S. S., 168
Berliner, D. L., 88
*Berson, S. A., 163
*Berthault, J.-M., 354
*Berthould, E., 274
*Bichel, J., 273
*Bidyadhar, N. K., 164
*Bierich, J. R., 277
Biserte, G., 152
Black, A., 347
*Black, H., 163
Black, R. L., 78
*Blahoš, J., 163
*Blanquier, 278
Blatz, G., 82
*Blechman, W., 277
Bloch, K. J., 274
*Blodi, F. C., 273
*Blumberg, B. S., 160
*Blumencron, W., 172
Boisvert, P. L., 154
Boland, E. W., 76, 169
*Boni, A., 171
*Bonomo, L., 351
*Bosch, S. J., 158
*Bothier, F., 338
*Bouchet, F., 268
*Bouton, J., 273
Bradshaw, J. P. P., 163
Braun, H. J., 265
*Braun, M. S., 169
Braunsteiner, H., 77, 87 *bis*, *275
*Brecher, G., 351
Breton, A., 152
*Brichant, J., 350
Brine, K. L., 165
*Brodie, B. B., 342
*Brower, T. D., 274
*Brückner, C., 81
*Brunsting, L. A., 164
Bubnow, B., 346
Bunim, J. J., 274
*Bunsch-Welkens, K., 351
*Burby, G., 166
Burley, D., 75, 341
Burns, J. J., 342 *bis*
*Businco, L., 276
Butler, C. F., 162
Bywaters, E. G. L., 71, 72, 159, 162, 267

Cabannes, R., 73
Caciolo, 160 *bis*
*Candela, V., 75
*Canet, L., 338
*Capeller, D., Von, 86
Caplan, H., 345
*Carballido, A., 164
*Carlo, M. de, 354
Carmel, P., 155
*Carr, A. J., 164
*Casertano, F., 354
Castor, C. W., 161, *350
Catanzaro, F. J., 71
*Catlet, J. B., 268
Cattaneo, R., 151
*Cavallo, A., 278
*Cavazzuti, G. B., 86
*Caviglia, E., 81
*Cecchi, E., 351
Certonciny, A., *159, 161
*Cervini, C., 83, 278
Chabot, J., 352
*Chamorro, G., 86 *bis*
Chamovitz, R., 71
*Champion, J., 273
Chandler, G. N., 76 *bis*
*Chanes, R., 158
*Chaouat, Y., 158
*Chartier, Y., 270
*Chatel, A. de, 157
*Chevallier, M. J., 153, 354
Chévez, A., 151, 152, 266
*Chierego, G., 335
*Chmielowa, M., 75
*Chodera, A., 81
*Chorazak, T., 169
*Chrapowicki, T., 152, 153
Christian, C. L., 79, 167, *351
Chung Wu, 277
Clappier, M. H., 274
Clark, W. S., 165
*Clementi, R., 165
*Cleve, H., 87
*Cobb, S., 338
*Coburn, A. F., 278
*Codreano, 278
*Cohen, A., 271
*Cohen, E., 274
Coke, H., 335
*Colonna, L., 75
*Coltorti, M., 164
*Conners, J. J., 354
*Conté Lo Vullo, L., 276
Contreras, R., 151, 152, 266
Coodley, E. L., 89
*Copeland, G. D., 86
Copeman, W. S. C., 154
*Coquelet, M. L., 87
*Corcos, J., 168
*Cornille, C., 338
*Corti, L., 276
*Cossermelli, W., 153, 169
Coste, F., 155, 159
Costero, I., 151, 152, 266
*Coventry, M. B., 338
Cowling, D. C., 343
Craddock, C. G., 167
Crain, Darrell C., 340
*Cramer, Q., 81
*Crespo, I., 84
*Criep, L. H., 347
*Cruickshank, B., 354

*Daikos, G. K., 351
*D'Alotto, V., 164
*D'Ambrosio, R., 164
*Daneo, V., 162, 275
Darke, C. S., 80
Davis, E., 74
*Dayton, P. G., 342
Decker, B., 350
*Décourt, L. V., 153
De Forest, G. K., 154
*Dehant, J., 350
Deicher, H. R. G., 272
*Déjean, C., 273
Denson, K. W. E., 87
*Depraitère, R., 87, 275
*Dérot, M., 164
Deshayes, P., 155
*Deslous-Paoli, P., 87, 159
*Didisheim, P., 274
*Dinsmore, H., 268
*Disertori, A., 338
*Dissard, P., 165
Ditata, D., 155
*Dixon, F. J., 87
Doniach I., 159
*Donoso, H., 86
*Donovan, R. J., 152
Dougherty, T. F., 88
Dreschler, M., 273
Dubois, E. L., 164
Ducach, G., 163
*Ducange, H., 157
Duff, I. F., 161
Dulong de Rosnay, C., 80, *275
*Dupont, M., 162
Durant, J., *268, *269, 337
*Durupt, L., 158, 268
Duthie, J. J. R., 163

Eastham, R. D., 87
Edelman, G. M., 79, 172
Édel'man, Z. I., 150
Edström, G., 155, *268
Edwards, J. E., 345

Egghardt, F., 77, 87 *bis*
Einaudi, G., 268, 275, 351 *bis*, 354 *bis*
Eisenstadt, H. B., 338
Ekelund, C., 84
Ellis, F. A., 342
Ellis, P. J., 88
Engleman, E. P., 82
Enjalbert, M., 273
Eonhardt, H., 269
Epstein, B. S., 270
Epstein, J. A., 270
Epstein, W. L., 268
Erlendsson, F., 78 *ter*
Ernesti, H. J., 270
Etcheverry, R., 86, 90
Espino-Vela, J., 335
Evans, D. A., 87
Evans, J. A., 344
Eyquem, A., 275 *bis*

Fahey, J. L., 351
Fajers, C.-M., 172
Fallet, G. H., 165
Fanconi, G., 273
Farrington, J., 272
Faulong, L., 159
Federico, O. M., 153
Ferraris, F., 351
Ferreira, W. A., 273
Ferri, R. G., 169
Finkelstein, A. E., 168
Fischel, E. E., 75
Fontaine, G., 152
Ford, E. H. R., 348
Forestier, F., 87
Forestier, J., *87, *159, 161, *338
Fowler, W. S., 345
Francesco, R., 150
Franckson, J., 338
Frank, C. W., 75
Frank, E. L., 338
Franklin, E. C., 79, 154, 172, *275
Franco, J.-C., 275
Freese, A. S., 83
Freiberger, R. H., 170
Freitas, G. G. de, 162
French, A. J., 161
Freson, A., 160
Freyberg, R. H., 153
Friou, G. J., 167
Fritz, K. W., 265
Fuchs, W., 270, 351
Fuld, H., 153
Furber, S. E., 335
Fyler, D. C., 75

Gabay, S., 88
Gabor, G., 164
Galins, N., 85
Galletti, F., 169
Galli, T., 81
Garcia del Rio, C., 164
Garelli, R., 162 *bis*, 270, 275 *bis*, 351 *bis*
Garland, A., 277
Gaspárdy, G., 88, 275
Gatto, E., 165, 354
Gaucher, A., 159, *354
Gay, A., 354
Gedda, P. O., 171
Geidel, H., 351
Gelfand, L., 278
Geschickter, C. F., 85
Ghinamo, G., 354
Ghiringhelli, G., 269
Giddings, L. E., 153
Gillot, F., 73
Giordano, S., 75
Giuliano, G., 351
Glyn, J. H., 348
Goetz, B., 81
Goggio, A. F., 266
Goldin, M., 348
Goldman, J., 271
Goldman, M., 77
Goldthwait, J. C., 162
Golomb, M. W., 84
Gomelsky, J., 164
Gomes Meleiro, 273
Gonzalez, F., 163, 344
Goodman, H. C., 351
Gordon, E. S., 347
Gordon, S., 273
Gospodinoff, A., 83, 84
Graber-Duvernay, J., 160
Graham, W., 171
Gravdal, H., 341, *354
Gray, J. D., 351
Greene, K. R. C., 268
Greslé, C., 353 *bis*
Griffin, S., 337
Griffin, S. W., 168
Grove, W. J., 84
Guasch L, J., *153, 333
Guerin, C., 338
Gutman, A. B., 163, 342 *bis*
Guyot-Jeannin, A., 275
Guzman, C., 86, 90

Hackenbroch, M., 158
Hackett, E., 72
Hackett, G. S., 269
Hahn, P., 157
Hallidie-Smith, K. A., 72
Hamerman, D., 348
Hamilton, D. E., 162
Hammarsten, G., 275
Harding, J. R., 75
Harnagel, E. E., 336
Harnecker, J., 163, 344
Harriman, D. G. F., 163
Harris, R., 270
Harrison, J. W., 354
Hart, F. Dudley, 160, 341
Hart, M. F., 276
Harter, F., 347
Hartfall, S. J., 76
Hartmann, F., 164
Hartung, E. F., 75
Hasbani, J., 347
Hatfield, C. B., 352
Havez, R., 152
Hayes, M. L., 168
Headley, N. E., 169
Heaton, J. M., 271, 341
Hedberg, H., 166, *275
Heffron, P. F., 276
Heimer, R., 153, *350
Hellstrom, H. R., 274
Helmholz, F. H., 346
Hench, P. S., 277
Henderson, A. T., 84
Hennigar, G. R., 270
Henrard, A., 156
Henry, M., 337
Herfort, R., 340
Herman, J. B., 271
Hermann, I. F., 77, 274
Hernandez, F. A., 278
Herranz, G., 275
Herrera Ramos, F., 157
Hershberger, L. G., 88
Hibbitt, L. L., 336
Hilbish, T. F., 78
Hill, S. R., 336
Hioco, D., 353 *bis*
Hodes, P. J., 354
Hohmann, G., 159
Holborow, E. J., 276
Holley, H. L., *168, 336, 337
Hollister, L. E., 82
Holman, H. R., 272
Holten, C., 273
Horst, A., 350
Horwich, L., 153
Houli, J., 269, 338
Howland, W. J., 88
Hughes, L., 152
Hugues, J., 162
Hvid, N., 341

Ionova, I. A., 86
Irving, M., 348
Ivanov, K. P., 353

Jablonska, S., 346
Jacobs, J. E., 354
Jacqueline, F., *275 *bis*, *338
Jacquiez, J., 338
Jalil, J., 163
Jarniou, A.-P., 273
Jarrett, S. R., 338
Jasiński, K., 89
Jenkins, J. C., *88, 274
Jensen, C. E., 275
Jessar, R. A., 268
Jochweds, B., 341
Johnson, C., 88
Johnston, M. L., 337
Jokinen, E. J., 276
Joly, L., 277
Jonsson, E., 275
Julkuken, H., 164, 168, 169, 275
Jung, A., 165

Kain, T. M., 266
Kaipainen, W. J., 164
Kalliomäki, L., *88, 336
Kammerer, W. H., 170
Kanenson, W. L., 271
Kappang, K., 273
Kark, R. M., 84
Kassirskij, I. A., 353
Katalinić, V., 86
Kellgren, J. H., 266
Kelly, Le M. C., 278
Kelly, M., 337
Kelly, P. J., 270
Kemper, J. W., 170
Kendall, P. H., 276
Kerby, G. P., 351
Kerr-Taylor, H., 335
Kersten, I., 277
Kettner, D., 349
Keusenhoff, W., 269
King, S. H., 338
King, T., 162
Kirpilä, J., 166, *269
Kissane, J. M., 350
Klapper, G., 158
Klinger, J., 86
Klontzas, E. I., 351
Koskinen, H.-M., 168
Kovács, L., 87, 275
Krammer, F., 278
Krause, R. M., *153, 333
Krčilková, M., 75
Kroll, F., 268
Kron, K. M., 77, 274
Kuhlmann, F., 278
Kuhn, W., 347
Kuhns, J. G., 156
Kuipers, R. K. W., 268, 270 338
Kulonen, E., 274, 336
Kunkel, H. G., 79, 154, 172, 272, *275

Laine, V., 168, 275
Laitinen, H., 157
Lambert, R., 83
Lambiase, M., 164
Lannigan, R., 165
Lansbury, J., 267
Lapp, H., 73
Larson, D. L., 167, 273
Laurell, A.-B., 169, 275
Laurent, F., 159
Lavenne, F., 350
Lavicka, J., 157, 163
Law, D. H., 88
Layani, F., 158, 268, 270, 273
Leach, W. J., 273
Lebeurre, R., 338
Lecomte, J., 162
Lee, S. L., 166
Lefkovits, A. M., 81
Legnaioli, M., 276
Lehmann, C., 270
Leinøe, L. H., 278
Leja, Z., 81
Lejeune, E., 83
Leonowicz, K., 350
Lerner, E. M., 88
Lessof, M., 151
Lever, J. D., 348
Levernieux, J., 83, 343
Levin, W. C., 343
Lewis, A. J., 153
Lewis, J. H., 274
Lichtwitz, A., 353 *bis*
Lièvre, J.-A., 157, 354

*Li-Li, L., 351
*Lima Faleiro, A., 266
*Limarzi, L. R., 86
*Lindgren, G., 275
Lipkin, E. A., 160
*Lisker, R., 351
Ljubomudrov, V. E., 271
*Lockie, J. M., 354
*Lockie, L. M., 77, 81
Loitman, B., 84
*Lopetégui, A., 277
*Lorenz, E., 152
*Losada, M., 82, 86 *bis*, 90
Lospalluto, J., 165, *351
*Louis, J., 86
*Louyot, P., 157, 159, 354
*Lövgren, O., 268
*Luce, S. L., 168
*Lucherini, T., 83, 268, 278
Lukasiak, B., 346
*Lyell, A., 164

*Macaluso, M. P., 271
*McCarthy, T. F., 86
Machek, O., 160 *bis*
*McCoy, F. W., 273
McEwen, C., 155, *335
McGuckin, W. F., 350
Mackay, I. R., 343
McKenzie, B. F., 350
*Mackiewicz, S., 81
*McMahon, F. G., 347
McNeil, J. H., 336
*Maderna, A. M., 269
*Majkowski, J., 269
Mäkinen, P., 274
*Mäkitalo, R., 276
Malech, G., 73
Malmed, L., 348
*Malmgren, R. A., 351
*Manheimer, R. H., 268
*Mäniken, P., 81
Mannik, M., 165
*Marchena, E. R., 347
Marienfeld, C. J., 72
*Marinoni, G. F., 351
*Marrazzi, G., 162, 351
*Marshall, H., 88
*Marteau, R., 343
*Martelli, A., 278
*Martin, W. J., 270
*Martinez, J. A., 273
*Marvektad, S., 277
Masbernard, A., 339
Mason, H. L., 277
Mason, R. M., 339
Massell, B. F., *75, 265, 266
Massie, R. W., 74
*Mathieu, J., 354
*Matsubara, H., 351
*Matthies, H., 278
Mayeda, A., 80, *351
Mayne, J. G., 277
*Mazzei, E., 164
*Mazzeo, G., 351
*Medal, L. S., 351
*Meersseman, F., 350
Mendez-Bryan, R., 167
Menon, A. N. K., 272
*Merliss, R., 278
*Michon, J., 157
*Michotte, L., 157, 159, 275
*Miehlke, K., 277
Mikkelsen, W. M., 161
*Milch, H., 354
Miller, J. H., 158
Miller, J. M., 265, 266
Miller, R. D., 345
*Mink, I., 274
*Misra, D. P., 86, 269
*Mizraji, M., 84
Monroy, G., 151, 152, 266
*Monte, A. D., 158
*Monteiro Baptista, L. M., 273
*Montgomery, D. A. D., 1 58
Montgomery, W. W., 273
*Moreau, A., 273
*Moritz, U., 171, 275
*Moro, E. R., 86
*Morteo, O. G., 158
Mortimer, E. A., Jr., *153, 333
Moustardier, G., 80, *275
Mucci, M. B., 154
Muehrcke, R. C., 84
Müller, W., 347, 349
*Muller-Eberhard, H. J., 275
*Muranda, R. M., 90
*Muras, O., 164
Murray, R. S., 339
*Muzzio d'Amelia, J. C., 342

Nabarro, J. D. N., 276
*Nägele, E., 347
Nagy, Z., 163
*Nahas, V., 268
*Nallar, L., 342
*Nápoli, L., 172
*Nassau, E., 335
Nathan, D. J., 168
*Nava, P., 81
*Nebó, F., 342
*Neter, E., 274
Nettelbladt, E., *269, *275, 349
Nevzorova, T. A., 170
Nezamís, J. E., 88
Nézelof, C., 83
Nice, C. M., 272
Nickerson, S. H., 340
*Nicoll, C., 342
*Nicrosini, F., 89
*Nightingale, E. J., 165
*Nigro, N., 275
Norcross, B. M., 77, *274
Norton, T. H., 158
*Novák, J., 275 *bis*
*Nyfos, L., 158

Oates, J. K., *83, 339 *bis*
*Obach Benach, J., 169
O'Connell, D., 338
Oka, M., 268
O'Malley, W. E., 85
*Orloff, S., 351
Ory, M., 156
*Ott, V. R., 270
*Otto, W., 270
*Paciornik, I., 338
Pärtan, J., 80, 77, *172
*Palacín, A., 277
*Pancaldo, A., 347
*Pansu, D., 338
*Paola, D. de, 338
*Paolo, A. di, 164
*Paolo, E. di, 169
*Pao-Mei, W., 351
Parker, R. A., 276
Parkins, R. A., 267
Pasquier, P. du, 80, *275
Passarelli, E. W., 82
*Patzerowa, T., 152, 153
*Paul, W. D., 269
*Paulo, S., 342
Pavero, A., 81
*Paz, M., 172
*Pazderka, V., 275
Peak, W. P., 77
Pearson, C. M., 167, 272, 346
*Pekkarinen, A., 88
*Pelargonio, S., 75
Pelocchino, A. M., 151
*Pende, G., 165
*Perini, Luis E.. 273
*Peroni, R., 164, 273
Perrier, C. V., 352
*Peteghem, J. van, 354
*Petersen, V. P., 273
*Petrecca, L., 164
*Peyron, J., 270
*Piccinelli, O., 89
*Pieniażek, P., 171
*Pierce, E. L., 270
*Piguet, B., 171
*Pike, R. M., 81
*Pimpinelli, E., 269
*Pines, A. M. H., 158
Piñol Aguadé, J., 340
*Piqué, J. A., 342
Pirani, C. L., 84
Please, N. W., 162
Ploss, L. N., 84
*Plotz, C. M., 81
*Podliachouk, L., 275 *bis*
Pollak, V. E., 84
Polley, H. F., 277, *338
*Porrini, A., 158
Poske, R. M., 348
Potter, T. A., 156
*Prakash, S., 269
*Preux, T. de, 157
Prinotti, C., 151
*Przybyl, L., 81
*Puchol, J. R., 164
Pugh, D. G., 88
*Puig, P. G., 164
*Purriel, P., 164, 273

Quarti, M., 75
*Quirno, N., 158

Raffi, A., 73
*Rainero, L., 266
Rakita, L., *153, 333
*Rakos, H., 275
*Rameau, Mme, 338
Rammelkamp, C H., 7
*153, 333
*Ramos, J. M., 269
Ramsey, R., 160
Randall, E., 349
*Randolph, H. E., 278
Rantz, L. A., 349
Raoux, J. P., 73
*Ravault, P., 83
*Rechenberg, H. K. von, 17
*Regonesi, L. C., 90
*Reinhardt, F., 87
*Rhinelander, F. W., 338
*Ribeiro Santos, V. A., 273
*Ricciardi, G., 75
*Rice, F. A., 271
*Rich, W. G., 81
*Richter, A., 350
*Riffat, G., 83
Rigazio, G., 151
Rigler, L. G., 272
*Rimoldi, R., 269
*Ringenbach, C., 273
Riordan, D. J., 77
*Ripatti, N., 269
Rivelis, A. L., 170
*Rizza, O., 351
*Rizzi, D., 278
*Robecchi, A., 275, 343, 354
Robert, A., 88
*Roberts, A. E., 83
Roberts, R., *153, 333
*Robins, H. M., 81
Robinson, C. E., 335
Robinson, H. S., *172, 335
Robles Gil, J., 150
*Rocés, E., 277
*Rodnan, G. P., 84, 274
*Roimicher, S., 338
Romani, J. D., 352
Rosa, F. de, 273
*Rosenberg, E. F., 86
*Rosenfield, A. B., 152
*Rosławski, A., 81
*Rotes Querol, J., 83
Rottenberg, E. N., 345
*Roudier, M., 164
Rousso, C., 352
*Roy, S. B., 75
Rozansky, R., 74
*Rubens-Duval, A., 159, 277
*Ruiz Moreno, A., 158 *bis*, 163 *bis*, 172, 271 *bis*
*Ruutsalo, H.-M., 169
*Ryckewaert, A., 343

*Sabota, S., 354
*Sadre Alain, A., 269
*Sailer, S., 275
Sala, G., 170
*Salomone, P., 266
*Sanjurjo, L. A. C., 83
*Santamarina, V., 277
Sarles, H. E., 343
Sarrovy, C., 73
Saslaw, M. S., *278, 333
*Scano, V., 157
*Schäfer, R., 338
Scheff, G. J., 72

Scheiffarth, F., 275
Scherbel, A. L., 354
Schiavetti, A., 277
Schiavetti, L., *83, *84, 277
Schmid, F. R., 153
Schmid, J., 90
Schmidt, E. R., 354
Schmitzer, G., 165 *bis*
Schoger, G. A., 269, 270
Schuler, B., 269
Schulof, Ö., 350
Schupp, E., 347
Schuster, C. A., *153, 333
Schuster, H., 348
Schwartzmann, J. R., 338
Ščitkova, T. A., 352
Sember, J., 83
Sendra, L., 73
Serafini, L., 157
Sergio, M., 150
Serov, V. V., 168
Serra, C., 164
Serra Peralba, A., 171
Seven, M. J., 271
Sèze, S. de, 269, 338, 343
Sheenan, B., 163
Shichikawa, R., 80, *88, *268, 351
Shimuzu, G., 88, 268
Shou-Yen, K., 351
Shuster, S., 352
Sichère, R. M., 354
Silberberg, M., 338
Silberberg, R., 338
Silva, L., 86, 354
Simmons, N. S., 167
Simon, J., 81
Singer, J. M., 81
Slater, J. D. H., 276
Slocumb, C. H., 157, 277, 345, 350
Smith, J. E., 75
Smith, R. T., 77, 274
Snapper, I., 168
Sobel, H., 88
Sobota, S., 350
Solari, S., 81, 165
Soto, O. F., 82
Sparta, D., 338
Sparup, K. H., 270
*Spilsborghs, G., 342
Sprague, R. G., 88
Stahlman, M., 74
Stancer, S. L., 265, 266
Starnes, W. R., 336
Šťáva, Z., 345, *347
Steck, I. E., 84
*Steinbrocker, O., 168
*Stern, T. N., 86
Stewart, L. C., 274
Stillman, J. S., 162
*Stoia, I., 86
*Strazza, J. A., 270
Streitfeld, M. M., 333
Stubbé, L. T. F. L., 171
*Sulkin, S. E., 81
*Sullivan, P. B., 273
Sundblad, L., 349
*Svartz, N., 268, 275
*Svilokos, N., 157
*Swanson, J. N., 83
Szilárd, J., 350
Szinay, G., 163

Taft, L. I., 343
*Taillard, W., 338
*Takiuchi, K., 268
*Talbott, J. H., 343 *bis*
*Tanabe, S., 88, 351
Tange, J. D., 345
Tanner, M., 153, 155
*Tansini, G., 269
Tarakanov, E. I., 352
Tarantino, M., 75
*Taube, H., 278
*Taylor, S. M., 351
*Teotia, S. P. S., 269
Thomas, G. T., 71
Thomas, J. R., 81
Thomas, P. M., 276
*Thomas, W. A., 350
*Thune, S., 172
*Thürigen, G., 277
*Tichy, H., 172
*Tiilikainen, A., 168
*Tobin, W. J., 278
*Tondreau, R. L., 354
*Toone, E. C., Jr., 270
*Topaz, E. R., 84
Toro, R. A. del, 77, 274
Toy, B. L., 85
Traut, E. F., 82
*Traverse, P. M. de, 87, 275
*Treiber, W., 270
*Tritsmans, E., 275
*Troisier, O., 83
Tubiana, R., 83
*Tupman, G. S., 158
Tye, M. J., 343

Ulloa, A., *168, 336, 337
*Usohiaga, J. Luis de, 165

*Vachon, A., 154
*Vahia, M. de, 157
*Vailliaumey, I., 159
Vaisman, B. S., *153, 333
Vajda, G., 350
*Vallado, P. F. del, 270
*Vanslype, J., 275
*Vartio, T., 273
Vasama, R. I., 336
Vassena, E., 75
*Vaughan, J. H., 88, 277, 337
*Vazquez, J. J., 87
*Vendura, G., 157
*Verhaeghe, A., 338
Vernet, A., 276
*Verstraete, J. J., 275
Vesey, C. M. R., 340
*Vida, M., 87, 88, 275
Vignau, I., *153, 333
Vignon, G., *268, *269, 337, *338
Vilanova, X., 340
Villa, L., 170, *343
*Villiaumey, J., 277
*Vintera, J., 75
*Violanti, A., 84
*Virkkunen, M., 157
*Virtama, P., 157
*Vitou-Villeneuve, L., 338
*Vittorio, S. di, 354
*Vondráková, I., 75
Vorlander, K. O., 265
Vrai, L., 163, *164

*Waine, H., 81
*Waitt, P., 75
*Wallace, S. L., 270
*Wallace, S. M., 338
Wan Ngo Lim, 334
Ward, J. R., 154
Ward, L. E., 277
*Warum, F., 172
*Weiner, A. D., 338
*Weir, D. M., 276
*Weskott, H. R. A., 89
West, H. F., 169
White, H., 343
White, J., 158
Wiedermann, G., 77, 87 *bis*
Wilkinson, D. S., 340
*Williams, G. T., 268
*Williams, R. C., 88, 347
Williams, R. R., *88, 274
*Williams, W. O., 278
Willkens, R. F., 273
*Wilson, J. C., Jr., 270
Wilson, M. G., 334
Wiltner, W., 163
Winslow, W. A., 84
*Wöllner, D., 270, 351
Wolman, L., 80
*Wramner, T., 270
Wright, V., 76 *bis*

*Yalow, R. S., 163
*Yannicelli, E., 273
Yasuda, J., 80
*Yoder, F. D., 153
*Yonis, I. Z., 165
Young, A. C., 80, 339 *bis*
Yü, T. F., *163, 342, *342

*Zacharle, L., 275
Zammit, F., 159
*Zañartu, J., 86
Zarafonetis, C. J. D., 346
*Zavazal, V., 157
*Zeldis, A., 354
Zevely, H. A., 161
*Ziegler, D. K., 266
Ziff, M., 153, 155, 165, *351
*Zissu, I., 165
Zuckner, J., *157, 160 *bis*
*Zülch, K. J., 165

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CONTENTS

PAGE

Familial Incidence of Rheumatoid Arthritis. JOAN M. BARNETT, W. R. M. ALEXANDER, and L. J. F. DUTHIE 279

Acute Rheumatic Fever in Young Men. J. D. H. SLATER and S. P. MACKINTOSH 285

Differences between the Fever of Still's Disease and that of Rheumatic Fever. F. J. McMINN and E. G. L. BYWATERS 293

Salicylates and the Adrenal Cortex. M. J. H. SMITH 298

Experience with British Latex Suspension for Agglutination Tests in Rheumatoid Arthritis. HARRY GOLD 301

Evaluation of an Epidemiological Method. STEPHEN P. MALAWISTA, LAWRENCE B. BOSS, and S. WARREN SHIDS 305

Anti-Inflammatory Effect of Obstructive Jaundice in Rats. RONALD L. EVANS and RICHARD W. McCOLD 309

Urinary Indole and other "Shock's Reagent Reactors" in Rheumatoid Arthritis. MARTTI OKA and V. V. E. LEPPÄNEN 313

Importance of an Increased Gamma Globulin Level in the Determination of Gel Strength in Collagen Diseases. H. JULKUNEN and ANNA TUHKANEN 318

Comparative Study of the Haemagglutination Test and a Single Latex Fixation Test for the Detection of the Rheumatoid Factor. G. MORGAN 322

Comparison of Intra-Articular Cortisone Analogues in Osteo-Arthritis of the Knee. M. J. KING 325

Book Review 329

Canadian Rheumatism Association 329

Heberden Society 330

Ligue Européenne contre le Rheumatisme 332

Abstracts 333

Index 351

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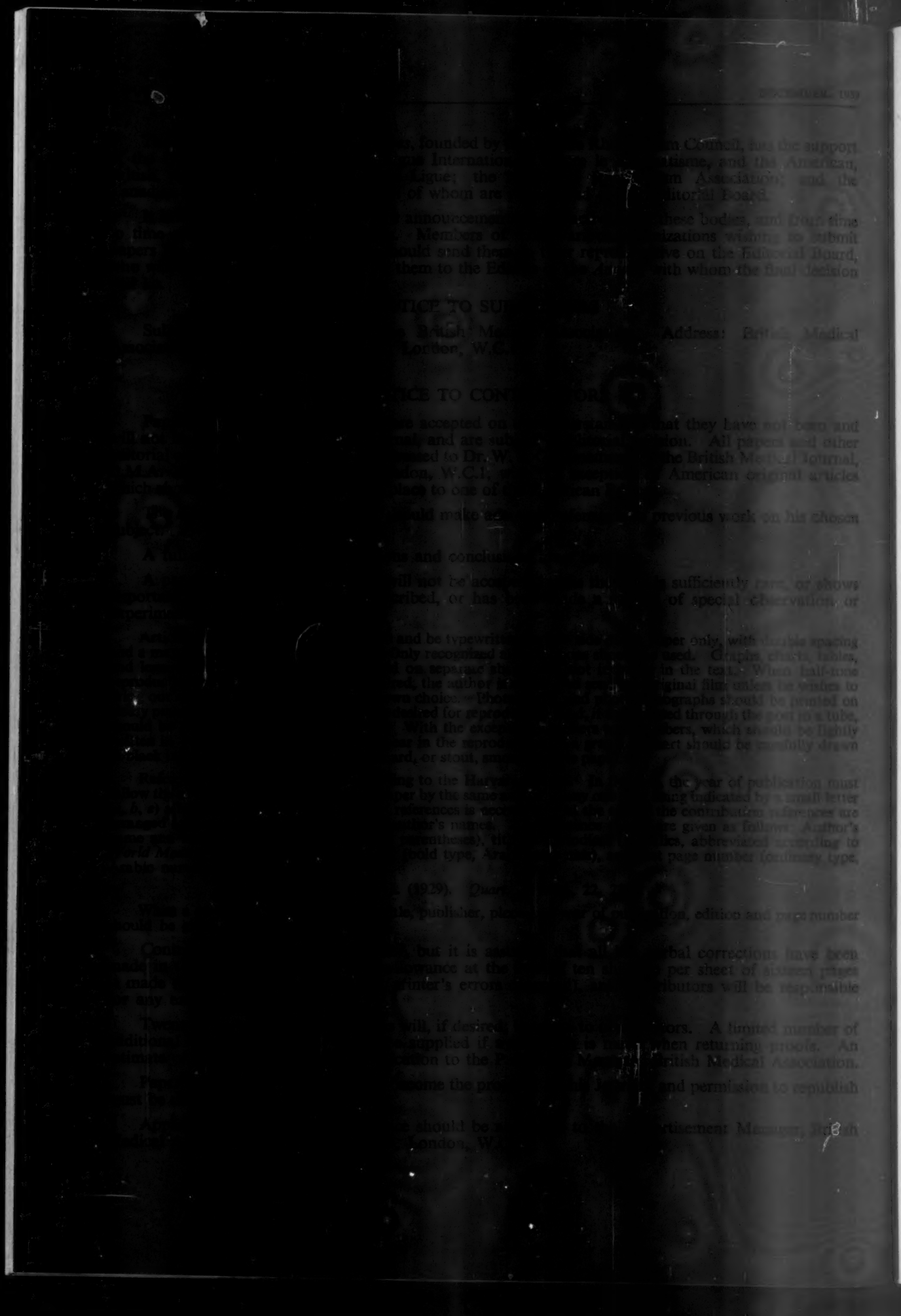

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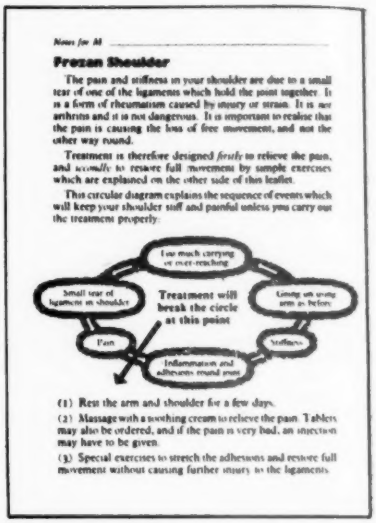
FROZEN SHOULDER

HELPING THE PATIENT TO HELP HIMSELF—AND YOU

Unless the patient understands his condition and can co-operate by carrying out exercises correctly from the start, frozen shoulder can be troublesome and persistent. The makers of Algesal Salicylate Cream have prepared a leaflet, with advice from a consultant in physical medicine, which describes the causes, nature and treatment of this condition. A series of simple, non-weight-bearing exercises, for restoration of mobility, are described in the leaflet, which is illustrated here.

Massage with Algesal for the relief of pain and spasm, completes the home treatment of frozen shoulder, which responds once the patient has learned to co-operate in doing the exercises regularly.

Other leaflets in this series deal with osteoarthritis of the knee, lumbo-sacral strain, and painful foot strain. They can be had on request, together with samples of Algesal, from E.G.H. Laboratories.



News for All

Frozen Shoulder

The pain and stiffness in your shoulder are due to a small tear of one of the ligaments which hold the joint together. It is a form of rheumatism caused by misuse or strain. It is not arthritis and it is not dangerous. It is important to realise that the pain is causing the loss of free movement, and not the other way round.

Treatment is therefore designed *firstly* to relieve the pain, and *secondly* to restore full movement by simple exercises which are explained on the other side of this leaflet.

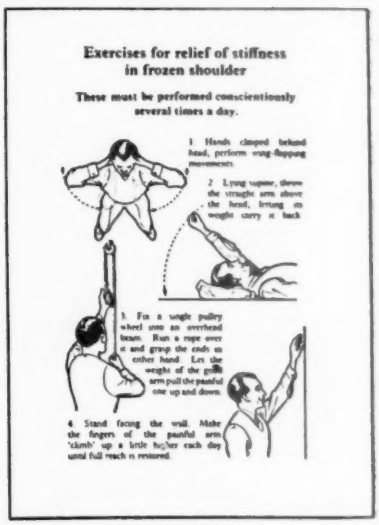
This circular diagram explains the sequence of events which will keep your shoulder stiff and painful unless you carry out the treatment properly.

Too much carrying or over-reaching
Small tear of ligament on shoulder
Treatment will break the circle at this point
Using arm as before
Pain
Stiffness
Inflammation and adhesions round joint

(1) Rest the arm and shoulder for a few days.

(2) Massage with a soothing cream to relieve the pain. Tablets may also be ordered, and if the pain is very bad, an injection may have to be given.

(3) Special exercises to stretch the adhesions and restore full movement without causing further injury to the ligaments.



Exercises for relief of stiffness in frozen shoulder

These must be performed conscientiously several times a day.

1. Hands clasped behind head, perform wing-flapping movements.

2. Lying supine, throw the straight arm above the head, letting its weight carry it back.

3. Fix a weight pulley wheel onto an overhead beam. Run a rope over it and grasp the ends in either hand. Let the weight of the [illegible] arm pull the painful one up and down.

4. Stand facing the wall. Make the fingers of the painful arm 'climb' up a little higher each day until full reach is restored.

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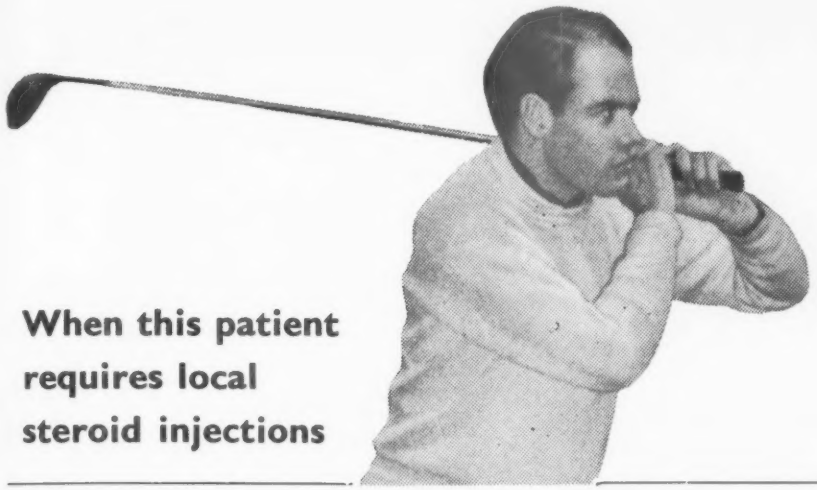

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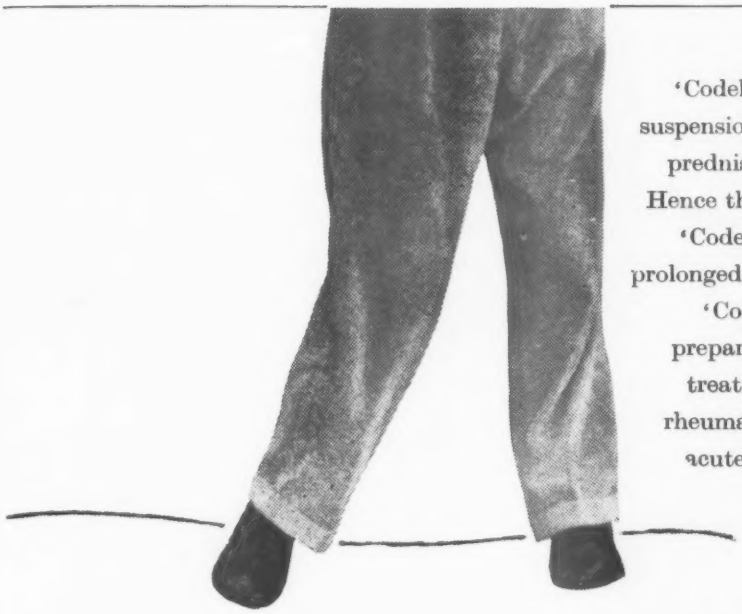

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Therapeutische Umschau 1952, 8, 143.

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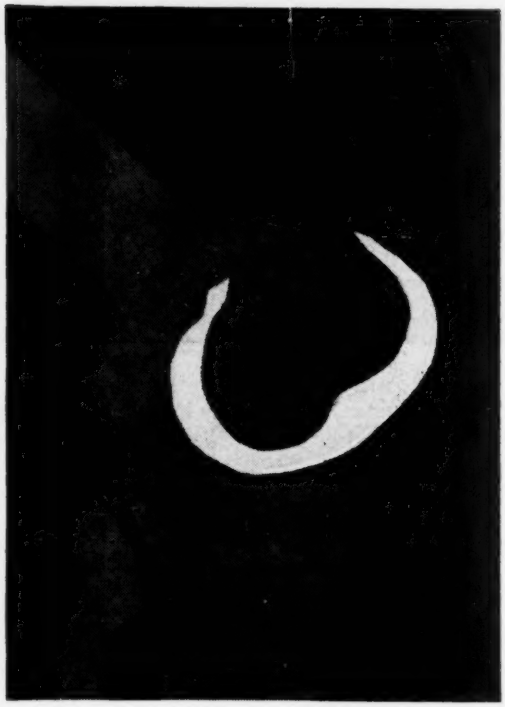

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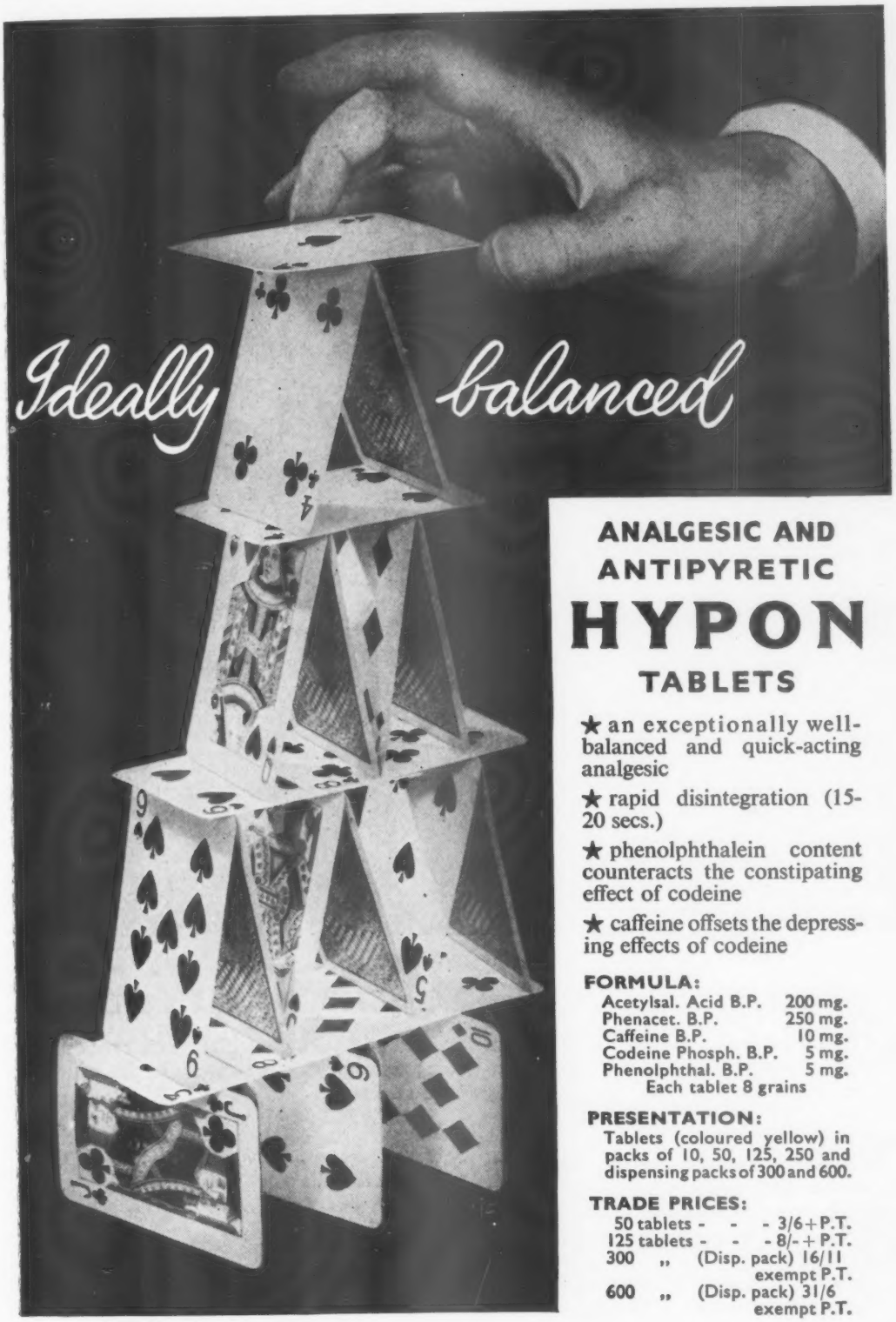

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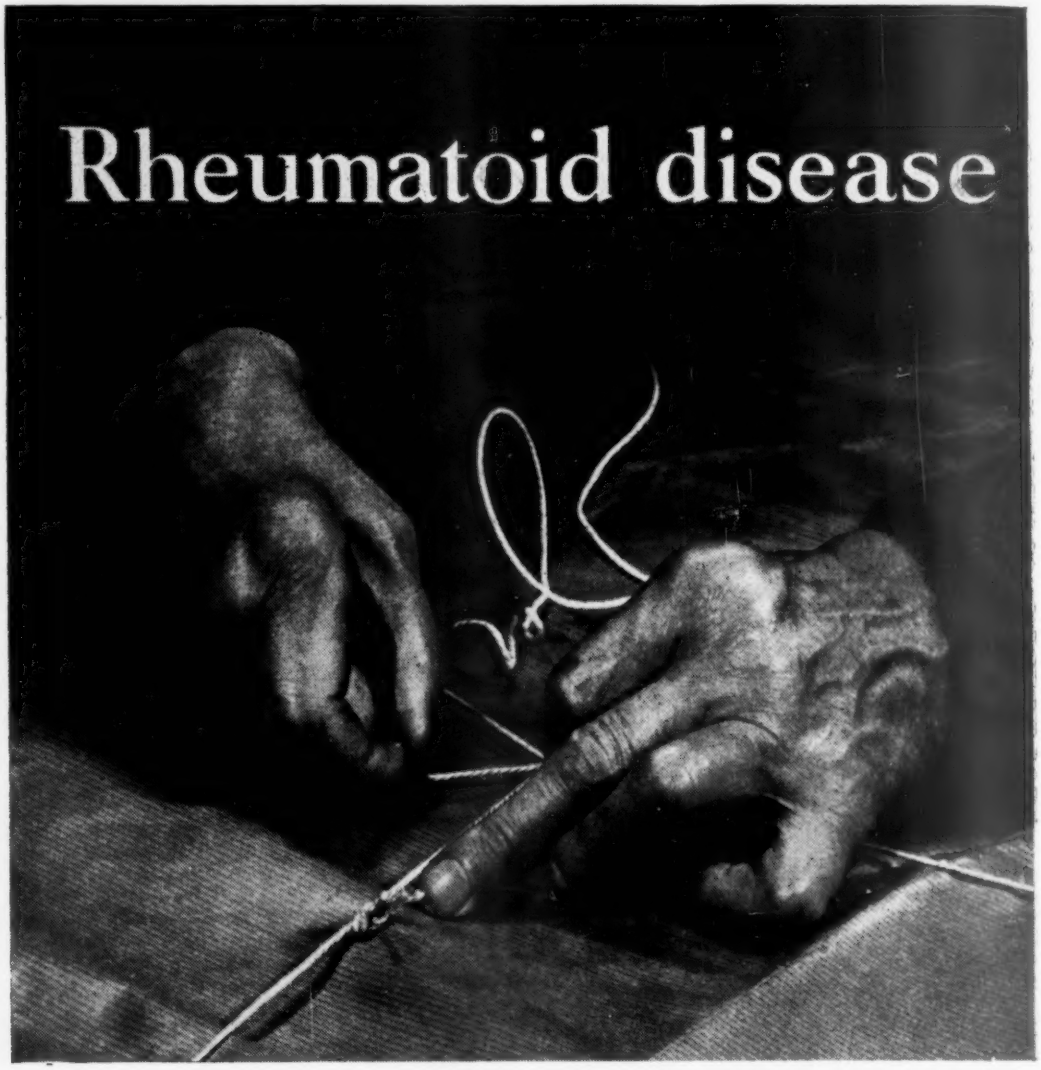

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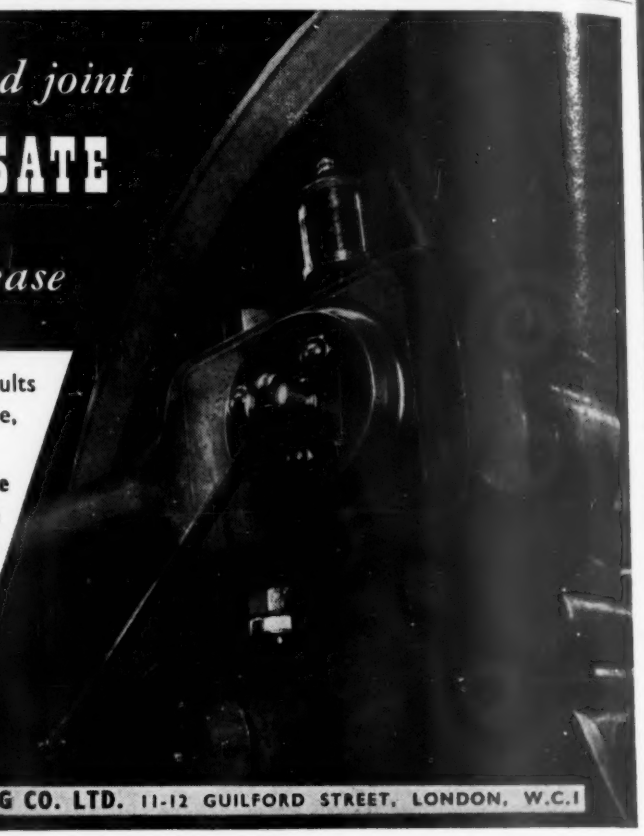

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